Functional recovery of sensorimotor and language networks

in patients with acute (sensorimotor)

and chronic (language) lesions

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Contents

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Summary

The human brain has the amazing potential to reshape itself following injury. The progress of cerebral damage (fast in acute brain lesion and slow in tumours) may influence the pattern of reorganization and the corresponding functional recovery. The present thesis aimed at investigating cerebral plasticity and the corresponding behavioural recovery with functional magnetic resonance (fMRI) in patients with acute or chronic lesions in both the language and motor network. Although a bulk of previous studies investigated the cortical activation pattern and the corresponding functional recovery in patients with brain lesions, there are still open questions concerning the extent to which contralateral brain structures are critically involved in functional recovery and how neurorehabilitation promotes improvement of function. These issues are still unclear in the field of language and motor functions, which share many aspects of functional reorganization. Therefore, we aimed at learning more about language *and* motor reorganization to both compare and differentiate the two processes against each other. Furthermore, we were interested in the comparison of functional reorganization in stroke and tumour patients because acute brain lesions cause damage to the brain within the time range of hours or days with probably different impact on language function than tumours, which slowly grow allowing a progressive redistribution of eloquent sites.

Pivotal for the interpretation of reorganization pattern in patients is the preceding assessment of the corresponding functions in healthy subjects to consider aspects of individual variability and task dependent differences in the neural representation of language and motor processes. Therefore we conducted two studies (1,3) where we investigated language and motor tasks in healthy subjects which were then assessed in patients with damage in the language (tumour and stroke, study 2) and sensorimotor network (study 4). Furthermore, the influence of additional therapeutical intervention (e.g. interactive cognitive therapy) on functional recovery and the corresponding activation pattern was assessed in patients from the acute state to a follow up period of three months (study 4). The main questions were which regions of the impaired language and sensorimotor network are activated in patients compared to healthy subjects and how the cortical activation pattern relate to the observed performance. The main goal of the thesis was to gain insight into plastic processes following brain damage and to compare the reorganization of different functions and etiologies of brain lesions and its impact on recovery. The findings of these studies should provide a better understanding of the many neuronal pathways that are available to sustain each type of language and motor task. Furthermore, the gained knowledge should also help better understand the influence of newly developed therapeutical interventions on these reorganization processes. The four studies are shortly summarized below.

Study 1: *Mapping of visual and auditory language processing by means of an fMRI protocol.* ***B. Keisker****, M. Meyer, S. Kollias, D. Weniger.* In this study, we used two language tasks in order to identify the distributed neuronal networks involved in visual and auditory word retrieval, with the aim of providing sound evidence that the two tasks qualify as fMRI protocol for presurgical language mapping. The protocol comprises two multimodal tasks known to assess different linguistic processing abilities. The picture word matching task consisted of line drawings of common objects presented together with a printed or spoken word that was either the name of the depicted object or of a semantically related object. The lexical decision tasks consisted of written or spoken words or pronounceable non-words. In the picture-word matching task, subjects had to decide whether the picture matched the word or whether the two line drawings (control task) were the same or not by pressing the corresponding button with the right index finger. In the lexical decision task, participants had to decide whether the stimulus item was a word or a non-word or whether the consonant strings contained a T. Overlapping responses in perisylvian areas were obtained across tasks and input modality, but there were also notable differences, pointing to an input specific and task dependent representation of language.

Author contributions

DW and BK designed and tested the experiments behaviourally. BK recruited the subjects, performed the experiments and analysed the fMRI-data. BK wrote the manuscript, which was corrected by DW, MM and SK.

Study 2: *Mapping of brain plasticity in stroke and tumour patients.* ***B. Keisker****, M. Meyer, S. Kollias, D. Weniger.* In study 2, patients with vascular brain lesions in the chronic stage and patients with brain tumors before and after surgical intervention were assessed with the two fMRI language paradigms described in study 1. The converging results have shown that reorganization patterns in stroke and tumour patients often include perilesional and right hemispheric language related areas with however different levels of effective functional recovery. The various behavioural deficits were dependent on the task itself (picture-word matching versus lexical decision), parts of the task demands (e.g. matching versus non-matching picture and word), input modality, and lesion site. There was no apparent difference between stroke and tumour patients in terms of reorganization patterns and the corresponding functional recovery. Effective integration of right hemispheric language related areas was observed in both groups, although there was a tendency for better behavioural performance in tumour patients.

Author contributions

DW and BK designed and tested the experiments behaviourally. BK performed the experiments and analysed the fMRI-data. BK wrote the manuscript, which was corrected by MM.

Study 3: *Differential force scaling of fine-graded power-grip force in the sensorimotor network.* ***B. Keisker****, MC. Hepp-Reymond, M. Meyer, A. Blickenstorfer, S. Kollias.* A visually guided motor task was designed to test the cortical representation of dynamic force generation with three different force grades (10%, 20%, 30% maximal voluntary contraction MVC). Brain responses were observed in the entire cortical and subcortical sensorimotor network and significant force-related modulation in several regions, including primary motor (M1) and somatosensory cortex, ventral premotor and inferior parietal areas, and cerebellum. The BOLD-signal however, increased monotonically with force only in contralateral M1 and ipsilateral anterior cerebellum. The remaining regions were activated with force in various nonlinear manners, suggesting that other factors, such as visual input, attention, and muscle recruitment also modulate the BOLD-signal in this visuomotor task. These observations may be of potential clinical significance in recovery following an infarct involving M1 in the sense that premotor and parietal cortical areas may poorly contribute to recovery in the control of low forces, whereas the anterior cerebellum with its direct peripheral input may play a primary role.

Author contributions

M-C.H-R. and SK designed the experiment. BK recruited the subjects, performed the experiments and analysed the fMRI- and behavioural data. BK wrote the manuscript, which was corrected by M-C.H-R, SK, MM and AB.

Study 4: *New technologies and concepts for rehabilitation in the acute phase of stroke: a collaborative matrix. E. M. Siekierka-Kleiser, K. Eng, C. Bassetti, A. Blickenstorfer, M. S. Cameirao, V. Dietz, A. Duff, F. Erol, T. Ettlin, D. M. Hermann, T. Keller,* ***B. Keisker****, J. Kesselring, R. Kleiser, S. Kollias, J. P. Kool, A. Kurre, S. Mangold, T. Nef, P. Pyk, R. Riener, C. Schuster, F. Tosi, P. F. M. J. Verschure and L. Zimmerli.*

The fourth study assessed three new applications of complementary technologies for acute phase in upper limb stroke rehabilitation. The developed therapeutically interventions are functional electric stimulation, arm-robot assisted therapy and virtual reality based cognitive therapy. A patient who underwent virtual reality cognitive therapy for two weeks showed change of cortical activation. The bilateral activation of the primary motor cortex during the visually-guided motor task, which was assessed in study 3, was present shortly after the stroke, but changed significantly toward normal ipsilesional activation. This shift of activation correlated with improved performance of the hand. The generality of this result, and the extent to which the VR cognitive therapy contributed to this result will be determined in future control tests with patients undergoing normal physiotherapy.

Author contributions

M-C.H-R., SK and BK designed the fMRI-experiment. ES-K and CB recruited the patients. BK performed the fMR-experiments and analysed the fMRI- and behavioural data. ES-K wrote the manuscript. The devices were developed by KE, TK, RR, PFMJV, MSC, RK, LZ, AD, FE, SM, TM, PP, FT and AB. The behavioural assessment of the patients was performed by ES, VD, TE, DMH, JK, JPK, AK and CS.

Zusammenfassung

Das Gehirn besitzt die bemerkenswerte Fähigkeit, sich nach einer Schädigung zu reorganisieren. Die Art der Umgestaltung und die damit verbundene funktionale Erholung werden möglicherweise vom zeitlichen Verlauf der Hirnschädigung beeinflusst. So kommt es bei einem Schlaganfall zu einer Läsion im Zeitraum von Stunden und Tagen (und den damit verbundenen akuten Beeinträchtigungen), während ein Hirntumor, wie beispielsweise ein Glioblastom, über mehrere Jahre unbemerkt wachsen kann, da sich die umliegenden Strukturen der Raumforderung anpassen können. Die vorliegende Arbeit hat zum Ziel, zerebrale Plastizität des sprachlichen und motorischen Netzwerkes mittels funktioneller Magnetresonanztomographie (fMRT) bei Schlaganfall- und Tumorpatienten zu untersuchen. Da die beiden funktionellen Netzwerke einige Gemeinsamkeiten im Prozess der Reorganisation aufweisen, wurde zerebrale Plastizität sowohl in der Sprache, als auch in der Motorik untersucht, um die beiden Prozesse einerseits miteinander zu vergleichen und andererseits gegeneinander abzugrenzen. Obwohl schon unzählige Studien die zerebrale Umgestaltung bei Patienten mit Hirnschädigung im sprachlichen und motorischen Netzwerk untersucht haben, bleibt immer noch unklar, welche der beobachteten Aktivierungsmuster massgeblich zur funktionellen Erholung beitragen. So besteht sowohl bei Patienten mit Sprachstörungen als auch bei solchen, deren motorische Funktionen beeinträchtig sind weiterhin die Frage, ob eine funktionelle Verbesserung auf den Einbezug der von der Läsion verschonten Hirngebiete auf der ipsiläsionalen (in der gleichen Hirnhälfte wie die Läsion) oder contralesionalen Hemisphäre (in der zur Läsion gegenüberliegenden Hirnhälfte) zurückzuführen ist. Um jedoch solche Reorganisationsprozesse und die damit verbundenen Aktivierungsmuster sinnvoll interpretieren zu können, ist es unabdingbar, sprachliche und motorische Funktionen vorgängig bei gesunden Probanden zu untersuchen. Somit können allfällige aufgabenabhängige und intra-individuelle Unterschiede in der neuronalen Repräsentation sprachlicher und motorischer Funktionen bei der Interpretation der Patientendaten berücksichtigt werden. Aus diesem Grund wurden zwei Studien mit gesunden Probanden durchgeführt. Dabei wurden einerseits Sprachaufgaben (Studie 1) und andererseits motorische Aufgaben und deren neuronale Korrelate untersucht (Studie 3). In den Patientenstudien wurden danach dieselben Aufgaben eingesetzt, um die Reorganisation des Sprachnetzwerkes nach Schlaganfall und Tumor (Studie 2) oder des motorischen Netzwerkes nach Schlaganfall (Studie 4) im Vergleich zu den gesunden Probanden zu untersuchen. Des Weiteren wurde in Studie 4 eine neu entwickelte Therapiemethode und ihr möglicher Einfluss auf die funktionelle Erholung und das damit verbundene Aktivierungsmuster untersucht. Zentrale Fragen der Arbeit waren: Welche kortikalen Regionen werden bei Patienten im Vergleich zu gesunden Probanden aktiviert? Wie weit korrespondieren diese Aktivierungsmuster mit den Verhaltensdaten? Im Wesentlichen sollten

diese Studien einen Einblick in plastische Prozesse nach einem Hirnschaden vermitteln und dabei einen Vergleich von funktioneller Reorganisation von Sprache und Motorik ermöglichen. Die vier Studien werden im Anschluss kurz zusammengefasst:

Studie 1: Die beiden in dieser Studie verwendeten fMRT-Sprachaufgaben sollten das neuronale Netzwerk, welches bei der visuellen und auditiven Wortverarbeitung involviert ist, aufdecken und somit auch als zuverlässiges Protokoll im Rahmen der prächirurgischen Operationsplanung etabliert werden. Die Sprachaufgaben wurden sowohl in der visuellen, als auch in der auditiven Modalität dargeboten und umfassten eine Wort-Bildzuordnungs- und eine lexikalische Entscheidungsaufgabe. Bei der Wort-Bildzuordnung wurden Schwarz-Weiss-Bilder zusammen mit einem geschriebenen oder gesprochenen Wort präsentiert, während die lexikalische Entscheidungsaufgabe aus geschriebenen oder gesprochenen Wörtern und „Nicht-Wörtern“ (z.B. Fuckel) bestand. In der Wort-Bildzuordnung musste der Proband entscheiden, ob das Bild mit dem auditiv oder visuell dargebotenen Wort übereinstimmt. In der lexikalischen Entscheidungsaufgabe hatten die Teilnehmer zu entscheiden, ob ein visuell oder akustisch dargebotenes Wort ein Wort oder „Nicht-Wort“ ist. Beim Lösen der einzelnen Aufgaben zeigten sich einerseits überlappende Aktivierungsmuster im perisylvischen Sprachgebiet, andererseits auch modalitäts- und aufgabenabhängige Unterschiede in der kortikalen Aktivierung.

Studie 2: In der Studie 2 untersuchte man Schlaganfallpatienten im chronischen Stadium und Tumorpatienten vor und nach dem operativen Eingriff mit den beiden fMRT-Sprachaufgaben, welche in Studie 1 getestet wurden. Die kortikale Reorganisation in beiden Patientengruppen umfasste sowohl periläsionale (direkt am Läsionsort) und contraläsionale der Sprachverarbeitung zugeordnete Regionen. Die funktionelle Erholung der einzelnen Patienten war jedoch verschieden stark ausgeprägt und war abhängig von der zu lösenden Aufgabe, der Präsentationsmodalität und der Läsion selbst. Schlaganfall- und Tumorpatienten unterschieden sich nicht wesentlich in bezug auf Reorganisationsmuster und funktionelle Erholung, wobei Sprachstörungen bei Tumorpatienten tendenziell weniger stark ausgeprägt waren. Eine erfolgreiche Integration rechtshemisphärischer Strukturen war bei beiden Patientengruppen zu beobachten.

Studie 3: Die kortikale Repräsentation von dynamischer Hand-Kraftgenerierung im Bereich niedriger Kraftstufen (10%, 20%, 30% der Maximalkraft) wurde mit einer fMRT Aufgabe getestet, bei der die Probanden durch visuelles Feedback geführt wurden. Diese Aufgabe war mit kortikaler und subkortikaler Aktivierung im gesamten somatosensorischen Netzwerk

verbunden. Durch Kraft modulierte kortikale Aktivität zeigte sich in verschiedenen sensomotorischen Arealen, wobei nur der primäre Motorkortex und das vordere Kleinhirn eine lineare Beziehung von Kraft mit der entsprechenden neuronalen Antwort zeigten. Eine mögliche klinische Implikation dieses Befundes wäre, dass eine durch eine Läsion im Bereich des primären Motorkortex beeinträchtigte Kraftkontrolle vorwiegend durch den Einfluss des Kleinhirns positiv beeinflusst werden könnte.

Studie 4: In dieser interdisziplinären Pilot-Studie werden drei neue Rehabilitationsmethoden vorgestellt, die komplementär zu bisherigen therapeutischen Anwendungen sind. Dabei handelt es sich um die sogenannte funktionelle elektrische Stimulation, die durch einen Armroboter unterstützte Therapie und eine kognitive Interaktionstherapie, die auf Methoden der virtuellen Realität basiert. Das kortikale Aktivierungsmuster eines Patienten, welcher die kognitive Interaktionstherapie absolviert hatte, veränderte sich von einer bilateralen zu einer ipsilateralen Einbeziehung des primären Motorkortex während der in Studie 3 getesteten Kraftaufgabe. Die veränderte kortikale Aktivierung korrespondierte mit einer verbesserten Handfunktion, es können jedoch erst weitere Vergleichsstudien zeigen, wieweit die kognitive Interaktionstherapie zu dieser Verbesserung beigetragen hat.

1 Introduction

Previous concepts of the functioning of the brain suggested a functional organization with both core areas where a lesion gives rise to neurological deficits and structures that are not essential for a particular function. However, the dogma of the static functional organization of the brain was called into question by reports of functional improvement following damage to eloquent cortical or subcortical structures (Duffau 2008). The advent of non-invasive neuroimaging methods allowed studying the mechanisms underlying these compensatory phenomena. In addition, neuroimaging studies investigating the neuronal representation for motor tasks in the primary motor cortex found support for the concept of distributed and overlapping representations rather than classical homunculus organization of single extremities and their corresponding movements (Indovina and Sanes 2001). These findings established the concept of cerebral plasticity.

Cerebral Plasticity is an intrinsic property of the nervous system retained throughout a lifespan (Pascual-Leone et al. 2005). It is defined as a "continuous process allowing short-term, middle-term and long-term remodeling of the neural organization, with the aim of optimizing the functioning of brain networks" (Duffau 2008). This dynamic process is the basis for all learning and adapting processes in response to environmental changes and pressures, physiologic modifications and experiences during brain development and ontogeny, but also during functional reshaping after brain damage (Duffau 2008; see also Pascual-Leone et al. 2005). Cortical plasticity as a fundamental process of learning has been studied with simpler motor tasks such as finger tapping (Koeneke et al. 2006) but also higher motor skills have been investigated in the context of musical proficiency (Jäncke et al. 2001. Münte et al. 2002, Schlaug 2001). Findings of these studies support the assumption that the organization of both representations of single muscles and complex movements in the primary motor cortex allows intrinsic reshaping of primary areas in motor learning processes.

This thesis however, focus on cerebral plasticity following vascular (language and sensorimotor network) and space occupying (language network) lesions. Since these two fundamental functions are predominantly affected by brain lesions the present work aimed to investigate plastic processes in both networks. In the following sections, the neurobiological and anatomic processes underlying plasticity at different functional levels will be reviewed before various aspects of human plasticity are discussed, in particular the reorganization of language and sensorimotor networks following brain damage. Before the four studies (two language and two motor studies) will be presented, the method of functional magnetic resonance, which has been used in all studies will be introduced.

The following sections about the neurobiological processes of plasticity predominantly discuss findings of animal research since it is hard to get insights into cellular processes of living humans. However, as recent findings of stoke studies have demonstrated (Di Filippo et al. 2008), much of the knowledge concerning the molecular processes of cerebral plasticity is also relevant in humans.

1.1 Mechanisms of Neuroplasticity

Cerebral plasticity is induced by various neurobiological and anatomic changes and includes processes as activity dependent synaptic changes, the unmasking of pre-existing synapses or the sprouting of new axonal terminals (Duffau 2008; Hallett 1999; Rossini and Dal Forno 2004). Much of the (animal) research on synaptic plasticity is based on the postulate of Hebb (1949) who proposed that, when a neuron repeatedly takes part in the activation of another neuron, the efficacy of the connections between these neurons is increased. Such specific sets of strongly connected neurons represent movements but also objects and more abstract entities of thought. Following brain damage, plastic reorganization of these cell assemblies can be achieved by spreading activity along the strong mutual synaptic connections (Wennekers et al. 2006).

1.1.1 Short-term plastic changes

Most forms of short-term synaptic plasticity are triggered by short bursts of activity causing a transient accumulation of calcium in presynaptic nerve terminals. This increase in presynaptic calcium in turn causes changes in the probability of neurotransmitter release by directly modifying the biochemical processes that underlie the exocytosis of synaptic vesicles (Citri and Malenka 2008). An important function of short-term synaptic plasticity is to influence the synaptic processing of information, enabling them to act as filters with a wide range of properties. Synapses that facilitate release of neurotransmitters during high frequency action potential bursts act as high-pass filter whereas synapses that relay low-frequency activity have a function as low-pass filter. The filtering characteristics of a synapse can be adjusted through modulation of the initial release probability. Most commonly, it occurs due to the release of neuromodulators that, via activation of pre-synaptic receptors, reduce the probability of release. Due to the changed synaptic filtering characteristics facilitation becomes predominant over depression. In this way, pre-synaptic disinhibition can convert a synapse from a high-pass to a low-pass filter (Citri and Malenka 2008). The unmasking of silent areas through dis-inhibition can cause a rapid reorganization of the functional network

1.1.2 Long-term plastic changes

Long-term synaptic plasticity has been extensively studied and often demonstrated through the processes of Long Term Potentiation (LTP) and Long Term Depression (LTD) representing an increase and a decrease of the efficacy of synaptic transmission (Hallett 1999; Rossini and Dal Forno 2004). The process of long-term potentiation is based on an increased simultaneous stimulation of two cells leading to longer-lasting plastic changes. In contrast, LTD is the weakening of neuronal synapses due to either strong synaptic stimulation (as it occurs in the cerebellar Purkinje cells) or persistent weak synaptic stimulation (as in the hippocampus). LTD lasts for hours or days and is thought to result from changes in postsynaptic receptor density, although changes in presynaptic release may also play a role.

Beside these neurophysiological changes, there are processes on the anatomical level as the sprouting of axonal terminals and the formation of new synapses that play a role over a longer time frame. These changes on the ultra-structural microscopic level might induce macroscopical processes such as reorganization of functional networks due to the recruitment of pathways that are functionally homologous but anatomically distinct from the damaged or non-functional areas (Duffau 2008; Rossini and Dal Forno 2004). In the following section various aspects of reorganization processes of functional networks are reviewed.

1.2 Cross-modal compensatory plasticity

Processes of compensatory plasticity have been documented in several studies assessing patients with deprived visual or auditory capabilities (Bavelier et al. 2006; Collignon et al. 2007; Finney et al. 2001; Noppeney et al. 2005; Pascual-Leone et al. 2005; Proksch and Bavelier 2002). Proksch and Bavelier (2006) found enhanced modulation of spatial attention and the remaining visual modalities in congenitally deaf individuals during a visual distraction task. The shift in distribution of attention was related to greater recruitment of multimodal brain areas including higher association and early sensory cortices as the secondary auditory cortex, the posterior superior temporal sulcus and the posterior parietal cortex. Similarly, Finney et al 2001 report activation of right auditory cortex in deaf subjects during processing of visually presented moving dot pattern (Finney et al. 2001). However, activity in auditory or visual areas in deaf or blind subjects at best establishes an association between activity in a given network with task performance but fails to prove that this activity is necessary for the sensory processing (Pascual-Leone et al. 2005). Clinical evidence for an existing relationship between occipital cortex activity and the ability to read Braille was provided by a tragically case report (Hamilton et al. 2000). A congenitally blind woman and highly proficient Braille reader was rendered unable to read Braille following a bilateral occipital stroke despite intact

somatosensory sensation and peripheral motor and sensory functions. A further prove of cross-modal plasticity was shown in the elegantly designed study of Collignon et al. 2007 assessing early blind individuals with a prosthesis which replaces vision with audition (PSVA) during recognition of bi-dimensional shapes. The application of disruptive TMS (transcranial magnetic stimulation) pulses to the right dorsal extrastriate areas affected the use of PSVA and auditory spatial location performance. The authors concluded that early visual deprivation leads to cross-modal reorganization in the processing of auditory information and auditory-to-visual sensory substitution.

On the structural level, Noppeney et al. (2005) investigated neuronal plasticity in visually deprived individuals. They found that early onset blindness alters the structure of the human brain in terms of gray and white mater changes within the visual somato-sensory and motor systems. Reduced gray matter volume in the visual cortex was interpreted as result of disuse whereas the increased size of white matter tracts of primary somatosensory and motor cortices was suggested to represent experience dependent plasticity (Noppeney et al 2005).

1.3 Plasticity in the language network

In order to understand various patterns of reorganization in the language network it is pivotal to consider models of language processing in healthy individuals including the aspect of inter-individual variability and recent findings on the lateralization and connectivity of eloquent areas.

1.3.1 Models of language processing

First language models identifying the left hemisphere as relevant for language processing date back to the seminal reports of Paul Broca (Broca 1861) who describes the case of two patients with impaired language production related to a lesion in the left inferior frontal lobe (the third frontal convolution). In 1874, Carl Wernicke reported the case of two patients with a lesion in the left posterior superior temporal lobe suffering from impaired speech comprehension; however, unlike the aphasic described by Broca, they could speak fluently (Wernicke 1874). The findings were taken as support for the premise that cognitive functions could be localized to specific convolutions of the brain (see also Dronkers et al. 2007). Lichtheim (1885) extended this model and proposed that Wernicke's area represents the phonological lexicon storing permanent information about word sounds whereas Broca's area was thought to be relevant for speech planning and programming. This model proposes that language functions are localized in more or less discrete areas of the brain (Fig 1A). However, the localized brain theories have been challenged by Geschwind (1965) who outlined a disconnectionist framework where he stated that disconnection syndromes are higher order syndromes

resulting from lesions of white matter tracts and association cortices. With this work Geschwind re-established the idea of functional networks in the brain and paved the way for future connectionist brain theories.

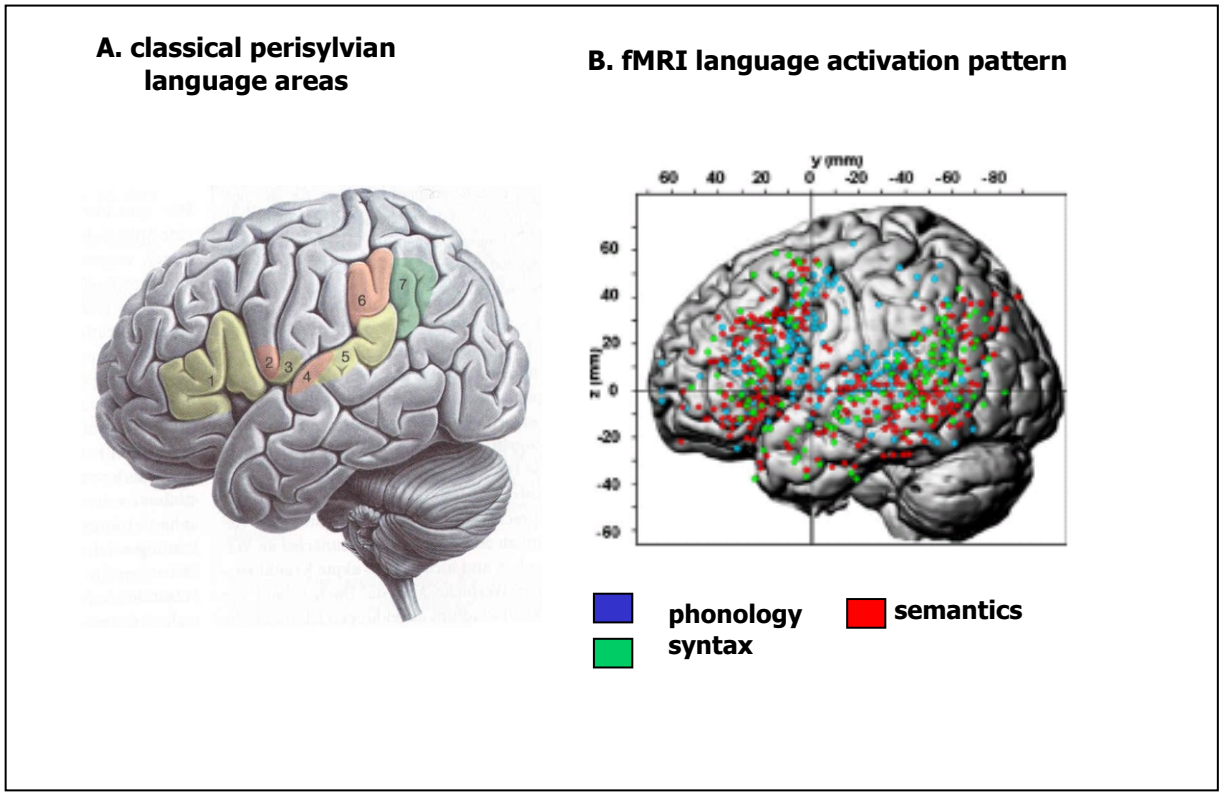


Fig 1 A. Classical perisylvian language areas *(Figure adapted from Nieuwenhuys et al. 1991)*. 2 B. Overview of the meta-analysis of left hemisphere language areas in terms of phonological, semantical and syntactical language processing. *(Figure taken from Vigneau et al. 2006)*.

The advent of neuroimaging methods in the 1980's allowed the non-invasive investigation of language processing and the previously assumed language organization has been reviewed in favour of more differentiated models of language processing that also account for aspects of inter-subject variability and context sensitivity of cortical activation pattern (see also Lee et al. 2006). Many brain imaging studies revealed that language function is represented in an interconnected fronto-temporo-parietal network (Fig 1B) (Specht et al. 2008; Hickok and Poeppel 2007; Meyer et al. 2004; Poeppel and Hickok 2004; Powell et al. 2006; Price 2000; Price et al. 2001) that varies across individuals from a mostly left to a bilateral to a right dominant representation (Hillis 2007; Seghier et al. 2008; Vigneau et al, 2006). This hodological view proposes distributed and parallel connected groups of neurons rather than individual centres (Duffau et al. 2005).

1.3.2 Language lateralization

A critical issue in fMRI-based assessments of language processing (e.g. lateralization) is the inter-individual variability of activation (Juch et al., 2005). Different factors may account for this variability; Considerable structural differences are found in regions subserving language functions; as demonstrated by Amunts and co workers (2004) Broca's region, comprising Brodmann areas 44 and 45, displays high intersubject variability with respect to size and shape of these two areas, to the sulcal pattern, and in the relationship of areal borders to surrounding sulci. A number of neuroimaging studies have reported sex differences, females displaying greater bihemispheric activation during language tasks than males (Kansaku et al., 2000; Pugh et al., 1996; Schlösser et al., 1998). But there is also neuroimaging data arguing against substantive differences between men and women in the large-scale neural organization of language processes (Frost et al., 1999). The authors of a meta-analysis of studies in which language-related activity was assessed with functional imaging techniques found no significant difference in language lateralization between men and women at the population level, but reasoned that it might be observed with some language tasks (Sommer et al., 2004; for a discussion of the inconsistent findings see Harrington et al. 2008). Another factor that may contribute to the variability of activation is the effect of aging upon the hemodynamic response measured by fMRI. (Huettel et al., 2001). Higher levels of activation have been found in Broca's and Wernicke's area in younger compared to older individuals (Rotte, 2005), healthy older individuals often showing compensatory recruitment of novel brain regions when performing on the level of their younger adult counterparts (Wingfield and Grossman, 2006).

1.3.3 Network of the functional anatomy of language

The functional framework of Hickok and Poeppel (2007) integrates neuropsychological, imaging and psycho-linguistic findings into one concept of language processing (Fig 2). The model primarily focuses on spoken language and suggests regions surrounding the primary auditory cortex to be the neuronal substrate of auditory language. Referring to findings of the functional anatomy of visual processing, they propose a similar organization of auditory language processing namely the differentiation into a dorsal and ventral stream. The earliest stage of cortical speech processing involves some form of spectrotemporal analysis, carried out in the bilateral auditory cortices. Subsequently the system diverges into two broad streams, a dorsal pathway and a ventral pathway.

The ventral stream serves as interface between sound-based representations of speech and their conceptual representations including widely distributed projections as parts of the sulcus temporalis superior, the gyrus temporalis medius and the gyrus temporalis inferior (posterior parts of the inferior temporal lobe). In contrast, the dorsal stream is crucial for the retrieval of

segmental aspects of the phonological language, e.g. if two words as 'arm' and 'harm' differ in their initial position/sound. It projects both to inferior parietal and to frontal regions and “provides a mechanism for the development and maintenance of 'parity' between auditory and motor representations of speech” (Poeppel and Hickok 2004: 67). The posterior part of the Sylvian fissure, in transition to the temporal lobe, is considered to be the interface of auditory and articulately coding.

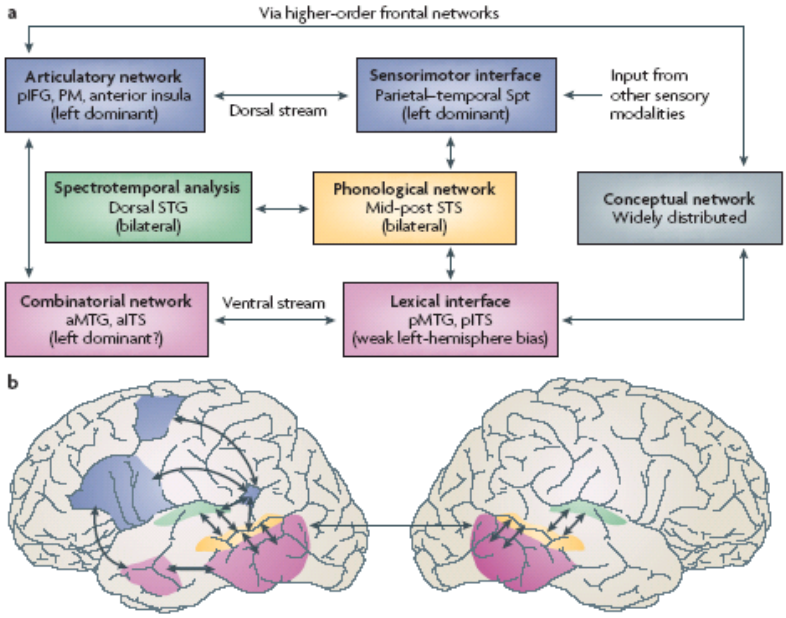


Fig 2. The dual-stream model of the functional anatomy of language. Explanation see text. *(Figure taken from Hickok and Poeppel et al. 2007)*.

The above described functional networks of language processing can be severely affected by brain damage. How such functional language networks are reorganized following brain damage (e.g. stroke and tumour) will be discussed in the following section.

1.4 Plasticity in acute brain lesions (vascular stroke)

Stroke as the third most common cause of death and also the most common cause of chronic disability has an impact on many activities of daily life. Brain functions such as language processing, sensorimotor integration, movement, walking and sensory perception may be severely affected (Warburton et al. 1999). The most common aetiology of stroke, middle cerebral artery infarction (MCA), is manifested by neuropsychological deficits such as aphasia and apraxia.

Since humans are essentially dependent on communication, life of affected persons changes in nearly all aspects of human interaction. In aphasic syndromes, expressive and receptive

language processing including speech, comprehension, reading and writing can be affected. However, there are patients with remarkable recovery of their language functions in the first two to three months, which gradually decreases in the following months. In the chronic state (12 months after onset), spontaneous recovery is reduced and diminishes whereas speech therapy is found to result in further improvement. In some patients however, the improvement involves communication abilities rather than language impairment per se (Cappa 2000). Spontaneous recovery depends on individual factors such as the characteristics of the lesion and the capacity of the persisting functional network involved in language comprehension and production (Calvert 2000; Heiss et al. 1999; Hillis 2007; Rijntjes 2006). The phenomenon of diaschisis demonstrated by early anatomical and neuroimaging studies, refers to regionally specific reductions in metabolic activity at sites that are remote from, but connected to damaged regions (Price et al. 2001). The term *dynamic* diaschisis, originally introduced by Price et al. (2001) describes the context-sensitive effects of a lesion on the evoked response of a distant cortical region that depends on interactions with the damaged region. Diaschisis has been considered to contribute to the global severity of the clinical picture after stroke, and its regression may be related to the clinical recovery (Cappa 2000). Recovery of aphasic symptoms goes along with a gradually reorganization of the damaged language system. The three possible forms of reorganization are restitution, substitution and compensation. In the case of restitution, residual tissue around the edge of the lesion, the so-called penumbra, allows some recovery of the affected language system (Hillis 2007; Wise 2003). A nearly complete recovery of damaged language abilities is possible with normalization of the functional metabolism (restitution). Homotopic cortex areas of the right hemisphere are often found to subserve language functions associated with the damaged left hemisphere regions. This is taken to be an instance of substitution.

However, the cerebral reorganization of language networks after stroke continues to be a matter of debate. The crucial issue remains whether language improvement represents sparing or restoration of function in perilesional zones of the left hemisphere or recruitment of homologous right hemisphere regions. There are several studies which support the (transient) involvement of the non-dominant right hemisphere in recovering language processing (Calvert 2000; Cao et al. 1999; Heiss et al. 1999; Hillis and Heidler 2002; Klein et al. 2002; Liégeois et al. 2004; Price and Crinion 2005; Richter et al. 2008; Romero et al. 2002; Saur et al. 2006; Thurlborn et al. 1999; Warburton et al. 1999; Weiller et al. 1995) whereas other studies suggest recruitment of perilesional areas during language processing as been being most efficient in regaining language (Heiss and Thiel 2006; Karbe et al 1998; Meinzer et al. 2008; Rosen et al. 2000; Spironelli et al. 2008; Zahn et al. 2002). E. g. Meinzer et al. (2008) report effective, treatment-induced functional reintegration of perilesional areas in chronic aphasics who underwent short-term intensive language training. In their longitudinal study assessing

aphasic patients with an auditory comprehension task, Saur et al. 2006 found three consecutive phases of recovery correlating with improved language function: a strongly reduced activation pattern of remaining left language areas in the acute phase followed by an additional recruitment of homologous language areas and finally a return to a predominant left hemisphere activation in the chronic phase (Fig 3).

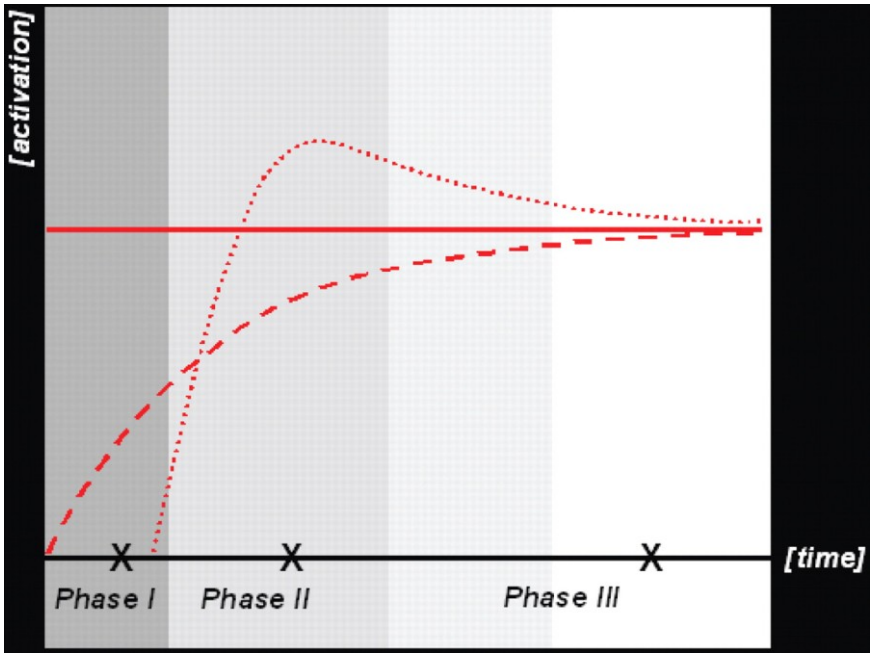


Fig 3. The three phases of language recovery after stroke: acute phase I, which is characterized by loss of function; subacute phase II, related to an upregulation of the language network; and chronic phase III, characterized by a consolidation and normalization of activation. The lines represent activation of control individuals (solid line), left language areas (dashed line) and right language areas of aphasic patients (dotted line). *(Figure taken from Saur et al. 2006)*

The role of the contralesional hemisphere for recovery remains controversial. It has been suggested that right hemispheric recruitment may reflect reliance on additional cognitive and linguistic resources which are not required by normal subjects during linguistic processes (Cappa 2000). There is also a debate whether this right sided language activity is because of a greater right hemispheric language function before the onset of the brain lesion or whether it is caused by the brain lesion itself. The latter case has been interpreted as phenomenon of transcallosal disinhibition probably reflecting less recovery than anomalous response caused by damage to the left hemisphere (Price and Crinion 2005; Winhuisen et al. 2007). However, there are studies that report right-hemispheric integration associated with improved language function in the acute and chronic state and before intensive therapeutical intervention within the chronic state (Richter et al. 2008; Winhuisen et al. 2005, 2007). The contribution of the right IFG to language recovery was investigated by Winhuisen et al. (2007). In nine patients, they applied 10 days and 8 weeks after stroke repetitive transcranial magnetic stimulation

(rTMS) to previously identified language regions in order to temporarily disrupt their function during a verb generation task and thus test the functional significance of these activated regions. RTMS adversely affected language function in all patients at both time points when applied over the left IFG, and in some of the patients over the right IFG. This suggests that the left IFG supports the verb generation task whereas the right IFG probably does not take over the function of the left IFG after stroke, but helps support the left language function (see also Crinion and Leff 2007). These findings support the hierarchical model of functional compensation following vascular brain damage as suggested by Duffau (2008), implying a recruitment of ipsilesional (especially peri-lesional) areas before the recruitment of contralateral homologous regions.

1.5 Plasticity in brain tumours

In contrast to acute brain lesions that cause damage to the brain within the time range of hours or days having a fundamentally negative impact on language function, tumor growth is slow and allows a progressive redistribution of eloquent sites and is therefore often not noticed over years. Only extensive neuropsychological assessments reveal slight cognitive disorders and more often epileptic seizures point to the existence of the place occupying lesion (Duffau 2008). There are different patterns of reorganization of the language networks during tumour growth. Either the function persists within the tumour or eloquent areas are redistributed perilesionally around the tumor. Another pattern is the recruitment of a widely distributed network within the lesioned hemisphere or the compensation by homologous language related areas. The latter compensatory strategy seems to be more effective in patients who experience language impairment developed over a longer time period (Duffau 2008; Thiel et al. 2005, 2006; Winhuisen et al. 2007) Finally, the combination of different patterns e.g. perilesional and contralateral reorganization of the language network can be observed (Duffau 2008). The role of the right Broca homologue area (right IFG) in speech performance of healthy subjects and left hemispheric tumour patients was tested by disturbing this region with rTMS during a verb generation task (Thiel et al. 2005). In all patients but not in controls, rTMS over the right IFG caused longer latencies and higher right hemispheric IFG activation. Application of rTMS over the left IFG also prolonged word generation latencies in all patients, indicating that this region is still essential for performance. In order to identify factors which determine the transfer of language function to the right hemisphere in patients with slowly growing left lateralized tumors, Thiel et al. (2006) assessed healthy and lesioned patients with PET and TMS during the performance of a verb generation task. Only patients with slowly progressing tumours recovered right-sided language function as detected by TMS. In patients with rapidly progressive lesions no right-sided language function was found and language

performance was linearly correlated with the lateralization of language related brain activation to the left hemisphere. The authors concluded that time is the factor which determines successful integration of the right hemisphere into the language network for compensation of lost left hemisphere language function in that slowly progressive brain damage and long disease duration allows the shift of language function to homologues areas.

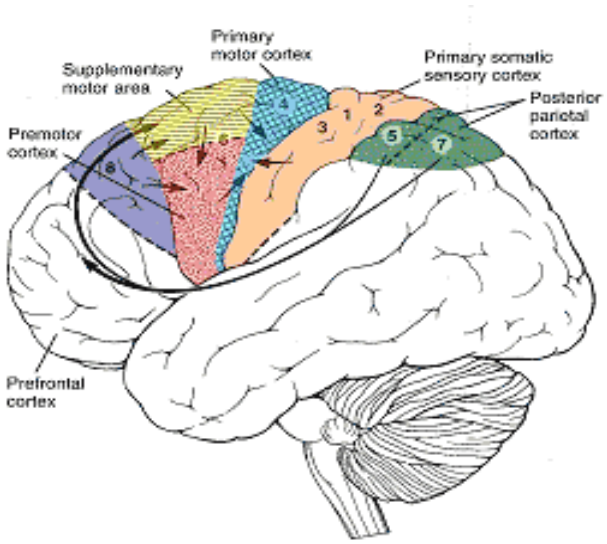
In this sense, cerebral plasticity in tumours can be described by a model of hierarchically organized processes, similarly to the reorganization processes observed in acute brain lesion, (Duffau 2008; Heiss and Thiel 2006). This model is predominantly valid for pre-morbid left lateralized language organization. Best recovery of function can usually be achieved after small brain damage by the restoration of the original activation pattern within the perilesional network of the dominant hemisphere. If primary functional centres are damaged, reduction of collateral inhibition leads to intrahemspheric compensation by secondary centres of the ipsilateral network which sometimes leads to incomplete but also often to satisfactory improvement of language function. In case of severely damaged ipsilateral language network interhemispheric compensation involving homotopic contralesional areas contributes to some improvement in function, but is usually not as efficient as intrahemispheric compensation except in patients with slowly growing tumours where language function can be shifted to the right hemisphere (Thiel et al. 2006). Patients, who have no highly lateralized language network premorbidly, probably show good recovery of language functions in spite of (extensive) damage to the left hemisphere.

1.6 Plasticity in the sensorimotor network

1.6.1 Physiology of sensorimotor brain areas

Motor activity and sensory feedback are fundamental processes for the functioning of (hand) motor control. Thereby the primary motor cortex is strongly modulated by the primary sensory cortex, which is the major source of sensory input. The sensorimotor network involved in motor control includes primary somatosensory, and secondary sensory and motor areas, which have a symmetrical organization in the right and left hemisphere. (Fig 4.).

Fig. 4. The motor areas of the cerebral cortex. Area 4 is the primary motor cortex. Area 6 on the medial surface is referred to as the supplementary motor area (SMA) and on the lateral surface as the premotor cortex (PMC). Areas 1, 2 and 3 belong to the primary somato-sensory cortex and 5, and 7 to the posterior parietal cortex. *(Figure taken from* www. Thebrainlabs .com /Images*).*



The components of the sensorimotor system form a hierarchy with multiple levels of control and the processing within these regions is critical for planning an action based on present perceptual information, past experience and future goals (Gazzaniga et al. 2002). Thereby, motor planning, perception and sensorimotor integration is controlled by the basal ganglia and thalamic relay circuits whereas supplementary motor and premotor cortices contribute significantly to motor preparation and execution via corticospinal fibres from the primary motor cortex under the parallel control of other descending systems. These processes of motor output and execution are constantly monitored by cerebellar relays. (Rossini et al.2003; Rossini and Dal Forno 2004), (Fig 5).

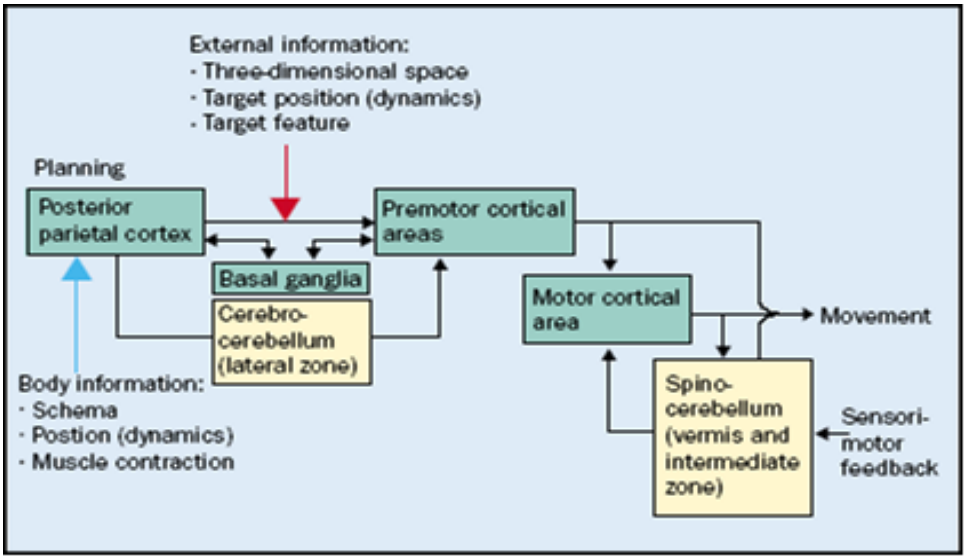


Fig 5. The role of sensory perception in motor learning includes large areas of primary somatosensory, visual, and motor cortices and secondary sensorimotor areas. Basal ganglia and thalamic relays contribute significantly to motor planning, sensory perception, and sensorimotor integration. Supplementary motor and premotor cortices have an important role in motor preparation and execution, via corticospinal fibres from the primary motor cortex under the parallel control of other descending systems. Cerebellar relays constantly monitor the motor output and motor execution. *(Figure taken from Rossini et al. 2003).*

1.6.2 Plasticity in acute brain lesions (stroke)

After middle cerebral artery infarction, the above described motor functions and somatosensation are most frequently impaired, either system may be affected preferentially (Rossini et al 2003). Recovery from the neurological deficits after stroke occurs over weeks or months and is often attributed to mechanisms of neuronal reorganization. However, recovery can vary greatly, particularly among patients with identical severity of symptoms in the acute phase (Rossini and Dal Forno 2004). Several reasons for these differences have been proposed including resorption of perilesional oedema, variability in the collateral circulation of the hypoperfused territories as well as the capacity of the human brain for functional reorganization. Increased excitability of the unaffected hemisphere is probably due to reduced transcallosal inhibition from the damaged hemisphere and increased use of the intact hemisphere (Liepert et al. 2000; Pascual-Leone et al. 2005). In the acute phase after stroke, the increased inhibition can be explained as a neural attempt to control perilesional activity in that oxygen and glucose demands in the penumbra of the stroke are reduced and thus limited (Pascual-Leone et al. 2005), (Fig 6).

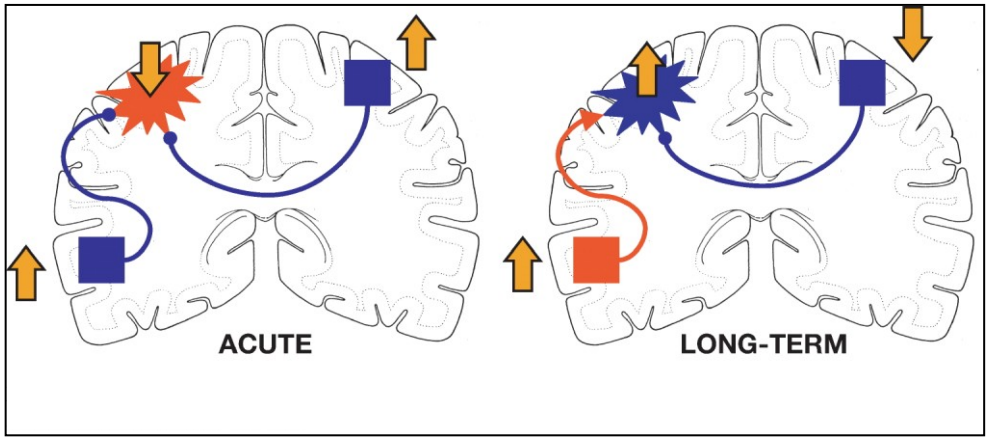


Fig 6. Schematic illustration showing that in the acute phase after a stroke, increased inhibitory input (within or across the hemispheres) may limit the extension of the lesion. Increased excitability (increased glutamatergic activity and reduced GABAergic activity) and postischemic LTP harbor an otherwise increased risk for further damage. However, after the acute phase, and once the injury is stable (long-term), excitatory input increases excitability and maybe further increase the efferent (e.g., motor) output. In contrast, inhibitory input at chronic stages is a maladaptive strategy, and the resulting functional outcome may be undesirable, with limited behavioural restoration. (*block arrows indicate a desirable increase or decrease in excitability; picture taken from Pascual-Leone et al. 2005).*

Thereby, the functions of the lesioned area are progressively adopted by parallel motor circuits. These parallel circuits may originate from the contralateral, undamaged primary motor area, bilateral premotor areas, bilateral supplementary motor areas and bilateral somatosensory areas. The existence of multiple yet discrete efferent microzones and macrozones form primary motor cortex was demonstrated by animal studies showing that a particular movement can be elicited through stimulation of different regions of the primary

motor cortex, often several millimetres apart and separated by nonresponsive districts (Donoghue et al., 1992; Merzenich and Jenkins, 1993). In addition, neuroimaging studies investigating the neuronal representation for motor tasks in the primary motor cortex found support for the concept of distributed and overlapping representations rather than classical homunculus organization of single extremities and their corresponding movements (Indovina and Sanes 2001). E. g. limb joint as shoulder, elbow and wrist are represented in the cortex more than once, but with different contiguity (shoulder to wrist, shoulder to elbow etc.). This parallel organization allows various forms of target-muscle activation resulting in different movement combinations (Rossini et al., 2003).

After the acute phase excitatory input to the perilesional area would seem to be best to maximize the capability of the preserved neurons in the injured tissue to strengthen functional recovery. In this phase, there is a shift of inhibitory interhemispheric and intrahemispheric to excitatory interactions. As long as efferent, cortico-spinal output pathways exist, reorganization will predominantly evolve in the involved functional network (Pascual-Leone et al., 2005). In fact, several studies have shown that task-dependent activation in the affected hemisphere seems to be predictive of good recovery, whereas recruitment of the non affected hemisphere may also correlate with less effective cortical plasticity (Kelly et al., 2006; Bütefisch et al., 2005; Calautti and Baron, 2003; Hallett 1999, 2001; Hendricks et al., 2002; Rossini et al., 2003; Ward 2004; Weiller et al., 1999). Nair et al. (2007) investigated well-recovered stroke patients with functional magnetic resonances imaging while performing unimanual index finger and wrist movements. They found that a return of neural activation in the lesional hemisphere, evidenced by an increased BOLD signal in the lesional M1, seemed to be signature of motor recovery following stroke. Furthermore, they suggested that movements that recover later during the recovery process and those that involve fine motor control are represented by a larger network including the sensorimotor cortex, SMA and cerebellum compared to movements that recover earlier.

Behavioural motor therapy has an influence on functional recovery in that it may also shifts cortical excitability balance between hemispheres. E.g. constraint-induced therapy, which implies the immobilization of the unaffected arm, has a beneficial effect on motor function by inducing a reduction of the excitability of the contralateral (undamaged) motor cortex and thus inducing a decrease in transcallosal inhibition. (Liepert et al., 2000, 2004). In the case of patients with highly paretic arm and hand, there are several new strategies that aim to augment the effects of practice. Beside the application of medications that alter levels of dopamine, norepinephrine or neurotropic factors in order to improve synaptic learning, there are new methods that support motor skill learning such as motor imagery or observation and task-oriented training in virtual environment. Ertelt et al. (2007) combined observation of daily life hand and arm actions with concomitant physical training of the observed actions in patients

with chronic motor deficit of the upper limb. The improvement of motor functions found in the course of a 4-week treatment lasted for at least 8 weeks after the end of the intervention. Repetitive stimulation of relevant muscles with functional electrical stimulation and practice of the paralysed limb with robotic assistive devices can also improve motor skills (see Dobkin 2008 for a review).

However, a detailed and systematic analysis of the cortical and subcortical representational changes underlying clinical recovery has not been undertaken so far. Moreover, despite increasing evidence that neurorehabilitation can promote clinical recovery (Dobkin 2004, 2008; Guadagno et al. 2003; Liepert et al. 2000, 2004; Miles 2005; Rossini and Dal Forno 2004; Sterr 2004; Teasell and Kalra 2004), the central correlates of neurorehabilitation treatments and their correlation with functional recovery have been scarcely evaluated. These investigations are important not only for understanding the physiological mechanisms of functional recovery but also for optimizing rehabilitation treatments and predicting outcomes and thus, are of essential clinical relevance for the patients.

The above sketched findings clearly indicate that ipsilesional (especially perilesional) but also homologues functional areas of the contralateral hemisphere are essential for the effective reorganization of either language or motor functions in acute (vascular) or chronic (vascular and tumour) brain lesions. However, there are still open questions concerning the extent to which contralateral brain structures are critically involved in functional recovery (language and motor network) and how neurorehabilitation promotes improvement of function (motor network). To further elucidate these questions, we conducted two studies in patients with either middle cerebral artery infarct or tumour affecting either language or motor function. The main questions were which regions of the impaired language and sensorimotor network are activated in patients compared to healthy subjects and how the cortical activation pattern relate to the observed performance. To appreciate the observed reorganization pattern, the designed language and motor paradigms were previously assessed with healthy subjects (study 1, 3).

Since all the four studies comprised the application of functional magnetic resonance imaging (fMRI), this method will be introduced in the next section before the single studies are presented.

2 Functional magnetic resonance imaging (fMRI)

2.1 Basic principles of magnetic resonance imaging

Magnetic resonance imaging provides a powerful tool to study anatomy and function of the brain. It is based on the resonance of atomic nuclei (e.g. hydrogen), the so-called nuclear magnetic resonance (NMR). The term resonance is defined as “increased amplitude of the oscillation of a system exposed to a periodic force, the frequency of which is approximately equal to the system’s natural frequency” (Mitchell and Cohen 2004). Hydrogen which is the most abundant element in the human body consists of a proton nucleus, carrying a unit positive electrical charge, and a single electron, which has a negative electric charge equal in magnitude to that of the proton. Most clinical magnetic resonance utilizes protons, but the nuclei of other common atoms such as sodium or potassium can also be used. MRI is possible due to some physical principles such as the reciprocal relationship between electricity and magnetism. Since the atomic nuclei of many atoms carry a small magnetic dipole moment, they experience an aligning force when exposed to magnetic fields. The magnetic field aligns protons along towards south or north pole of the field (Fig 7A). When north points to north and south to south, the magnets are in a high energy state. The net excess of protons aligned with the direction of the main magnetic field produces the so-called longitudinal magnetization. The rate at which a material approaches equilibrium is determined by a time constant known as its T1, which is characteristic of the material. T1 is the time required for about 63% of the magnetization to recover. The T1 relaxation time of different tissues varies from 100 ms for adipose tissue over 2 seconds for CSF and pure free water with 3 seconds. In contrast, cellular tissues tend to have much shorter T1 relaxation times than do fluids. If images are acquired with a series of RF pulses (the typical case), the time between successive RF pulses, called TR, determines the T1 weighting in the image signal: e.g. comparing two different tissues, the longitudinal magnetization of the tissue with the longer T1 (slower recovery) is less than that of the tissue with the shorter T1.

The quantum property of the atom nuclei, called *angular momentum*, is the tendency for a spinning object to continue to spin about the same axis. It prevents protons from simply aligning their magnetic axis with the external magnetic field. Instead they spin, or precces about it (Fig7 B).

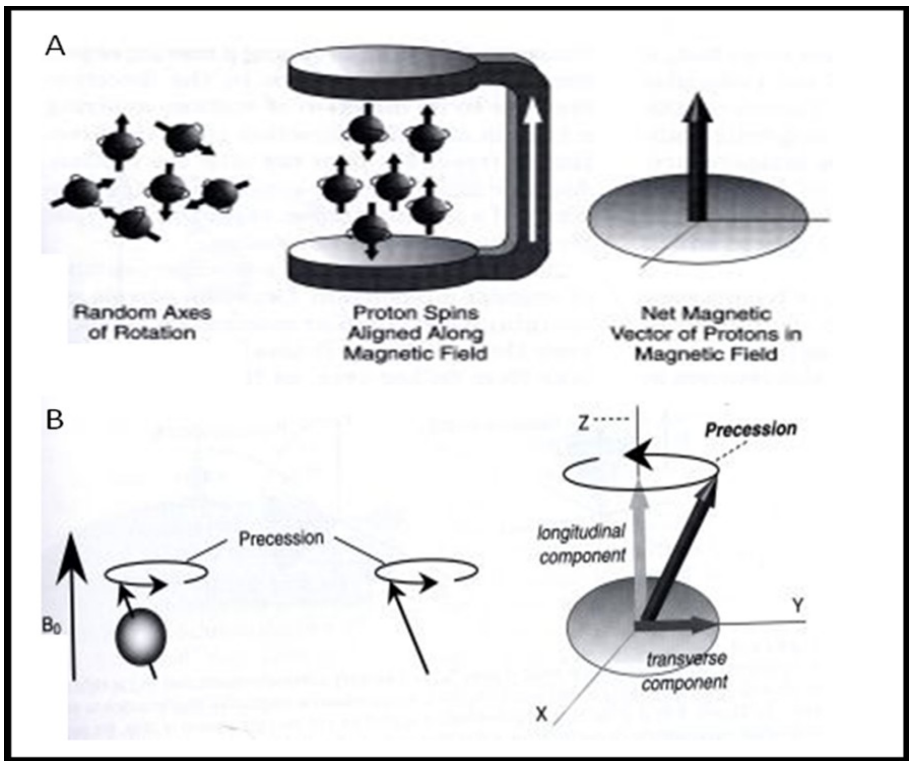


Fig. 7A. Proton rotational axis in the absence of a magnetic field (left) is random. In the presence of a magnetic field (middle), there is a net excess of protons aligned with the direction of the main magnetic field. This produces longitudinal magnetization (right). 7B. Each proton has a small magnetic field and a quantum property called angular momentum, or spin. Its angular momentum causes it to precess when it is placed in a magnetic field (B°). (*Figures taken from Mitchell and Cohen, 2004*).

The relation between the strength of a magnetic field and the rotational rate of the anatomic nuclei is of fundamental importance for MRI. The following equation represents the Larmor relation, where f is the frequency of rotation (the number of rotations per second), B the magnetic field strength, and y is known as the gyromagnetic ratio, which differs between various atom nuclei.

Larmor relation: $f=\gamma B$

2.1.1 Transverse Magnetization and T2 Contrast

Following excitation of protons aligned in the magnetic field B0 by a radiofrequency (RF) pulse, a signal is created with an amplitude that decays rapidly. The RF pulse is usually transmitted from a coil. Excitation of the protons by NMR produces a further magnetic field (B1) that oscillates at several million times per second, in the radiofrequency (RF) range. Because the magnetization has been forced out of its equilibrium longitudinal state, the protons are excited into a higher energy state. That means the B1 magnetic field rotates the

initially longitudinal (along B0 magnetization into the transverse plane, producing transverse magnetization). E.g. a 90° pulse rotates all of the magnetization into the transverse plane, eliminating the component along the longitudinal axis. However, this change in the magnetic orientation only occurs if the B1 magnetic field is rotating at precisely the same rate as the individual protons. This phenomenon is called resonance leading to the term nuclear magnetic resonance (NMR). Initially, after a 90° radiofrequency pulse, the magnetization from all protons in the sample is summed in the transverse plane and precesses together, yielding a large MR signal. Over time, differences in the local magnetic field cause the protons to precess at slightly different rates and they go out of phase which results in a loss of signal. Ultimately, the signal goes to near zero when the magnetization from individual spins is cancelled by oppositely directed spins. This transverse relaxation, which induces the decay of the MR signal is called the free induction decay" (FID). The term T2 describes the decay rate that is intrinsic to the tissue, thereby the signal decays to near zero after three or four T2 periods. The T2 of body tissues varies over a broad range, from less than a few milliseconds for bone to more than a second for simple fluids. To form an MR image, several milliseconds must pass between the end of the RF excitation pulse and collection of the MR signal. This time between the end of the RF pulse and signal collection is called echo time or time after excitation (TE) Fig 8.

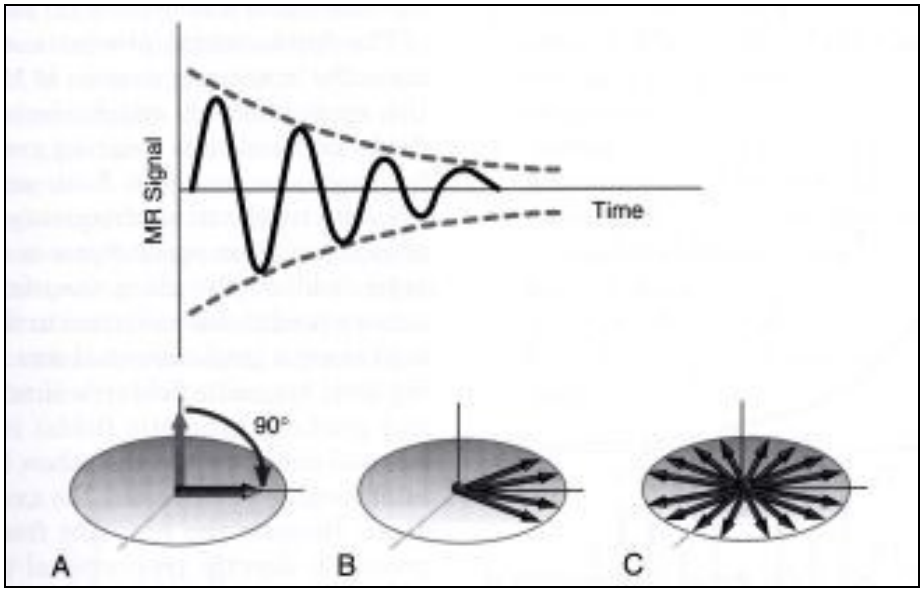


Fig. 8. The decaying magnetic resonance (MR) signal is represented as an oscillating wave, the magnitude of which is depicted as the space between the gray dotted lines. Initially, after a 90° radiofrequency pulse, the magnetization from all protons in the sample is summed in the transverse plane and precesses together, yielding a large MR signal (A). Over time, differences in the local magnetic field cause the spins to precess at slightly different rates and to go out of phase, resulting in a loss of signal (B). Ultimately (C), the signal goes to near zero when the magnetization from individual spins is cancelled by oppositely directed spins. The rapid decay of the signal is depicted at the top, which is called the free induction decay (FID). *(Figure taken from Mitchel and Cohen, 2004).*

2.1.2 Spatial Localization

Since the radio signal does not contain enough localization information, the application of supplementary magnetic fields the so-called imaging gradients is necessary. The application of the magnetic field gradient causes protons at one end of the gradient to spin slower and protons at the other end to spin faster. Thereby, the magnetic gradient produces a predictable variation in resonance frequency along the axis, because the resonant frequency of a proton is directly proportional to the magnetic field that contains it. This correlation allows determining the position of a proton. Magnetic field gradients are usually produced by gradient coils within the bore of the main magnet (Fig 9)

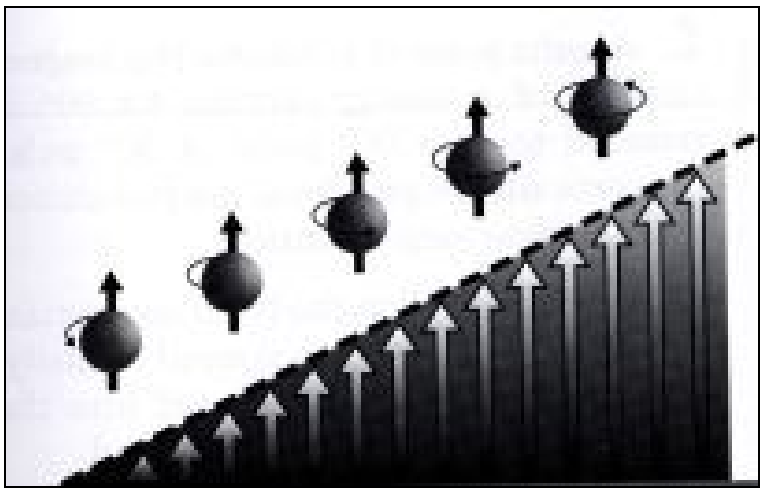


Fig. 9. Magnetic field gradient applied in addition to the homogenous main magnetic field. The magnetic field increases to the right along the axis of the gradient, increasing the resonant frequencies of the affected protons. *(Figure taken from Mitchell and Cohen, 2004).*

2.2 Functional magnetic resonance (fMRI)

The term “functional neuroimaging” primarily refers to the hemodynamic imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The continued technical and methodological progress in the technical capabilities involved in neuroimaging techniques within the last decade (particularly in terms of design and statistical advancements in data analysis, but also in improvements of temporal resolution) has led to an upsurge in studies utilizing these techniques. The utility of PET and fMRI in assessing cognitive processes arises from their ability to measure changes in blood-flow parameters, generally referred to as hemodynamic response (HR). That is, both PET and fMRI are reliant on blood-flow changes triggered by neuronal oxygen consumption. As there is a linear relation of increase in regional cerebral blood flow (rCBF) and neuronal activity, enlarged blood flow can be considered a reliable (indirect) indicator of increased neuronal activity in response to enhanced local oxygen demands.

In more applied terms, sensory and cognitive processes such as hearing involve the auditory cortex. When a person is presented with auditory stimuli, the neurons in the auditory cortex become excited, which also means they consume oxygen. In terms of cerebral metabolism, hearing is associated with locally enlarged oxygen consumption and increased blood flow, since fresh, oxygenated blood has to be delivered to the auditory region, in order to regain the former equilibrium. PET and fMRI are capable of indirectly measuring this oxygen and visualizing the brain regions that subserve certain sensory and cognitive activities by the use of colour-coded images of rCBF. Basically, PET and fMRI can show that a person's auditory cortex lights up while listening to music, sounds, or words. Besides mapping functional activation magnetic resonance imaging is capable of providing structural scans that visualize the brain's grey and white matter.

The last few years have seen a shift away from the use of PET towards fMRI because the latter provides significantly better temporal (in the range of 1 s) and spatial (in the range of 1 mm) resolution. Unlike PET, fMRI reveals fine details of anatomy, is not invasive, and does not expose patients to radiation. In general terms, magnetic resonance imaging takes advantage of the magnetic properties of cerebral tissues to generate functional and structural brain scans. Functional MRI, in particular, extends the structural capability of MRI by measuring the BOLD which relies on changes in the ratio of oxygenated to deoxygenated haemoglobin in the cerebral bloodstream. As a function of the loss of oxygen from haemoglobin during neuronal activity, the net amount of deoxygenated haemoglobin temporarily increases. Because deoxygenated haemoglobin is paramagnetic, a local concentration of deoxygenated blood causes magnetic field inhomogenities that are detected by the MR scanner. Thus, the paramagnetic properties of deoxygenated haemoglobin serve as indirect markers that help identify the locus as well as the strength of neural activation. The brain compensates for this net amount of oxygen concentration by supplying oxygenated blood with a time lag of 5 to 8 seconds. Again, changes in cerebral blood-flow patterns are considered to reflect simultaneously occurring neural activity, described by a process called neurovascular coupling, even though the precise link between cerebral blood flow and neural excitement is still to be clarified (Fig 10).

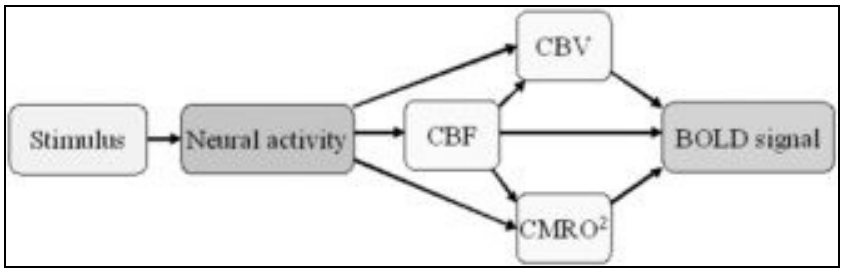


Fig 10. Neurovascular coupling. Schematic of the transformation of neural activity elicited by a stimulus to a hemodynamic response resulting in a BOLD signal. The BOLD signal reflects the ratio of nonparamagnetic oxygenated haemoglobin to paramagnetic deoxygenated haemoglobin. Neural activity alters this ratio by influencing several factors, including the CBF, CBV, and CMRO2. *(Figure taken from Price et al. 2006).*

The time course of the BOLD signal is in the range of seconds. An initial decrease of oxyhemoglobin due to the consumption of oxygen leads to the so-called initial dip of the BOLD-signal, which is followed by an increased blood flow leading to an increase of oxyhemoglobin. The excess of oxyhemoglobin compared to deoxyhemglobin causes the signal increase that peaks around 5-8 seconds after stimulus onset and returns to baseline after 10-16 seconds Fig 11.

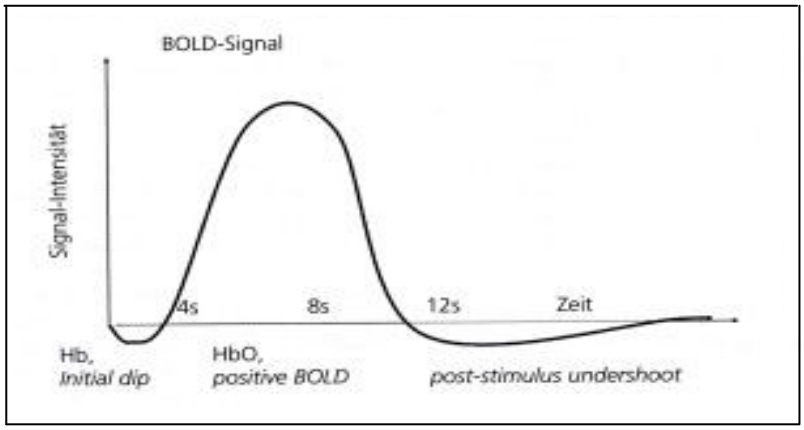


Fig. 11. Time-course of the BOLD-signal*. (Figure taken from Jäncke 2005)*

Unlike PET, fMRI is capable of detecting the hemodynamic response to one single transient stimulus presentation, which allows the application of trial-based or event-related rather than blocked paradigms (D'Eposito et al., 1999). As in behavioural studies, in event-related designs stimuli entailing different experimental conditions are presented in pseudo-random order. Single trials of a particular stimulus are presented, and then the responses are averaged time locked to the stimulus presentation. However, given the temporal characteristics of the hemodynamic response, two succeeding stimuli have to be sufficiently dispersed by 4 to 8 seconds to avoid overlap of succeeding responses.

In the following sections, the different aspects of the analysis of the experimental data are shortly summarized.

2.2.1 Pre-processing in fMRI

Since the experimental data shows components that are not task-related, they have to be removed in order to get an image of higher quality. The so-called signal-to-noise ratio (SNR) is the quotient between task-related variability and non task-related variability and provides information concerning the quality of the data. The pre-processing steps, which aim to remove as much as possible of the non task-related variability, are shortly described in the following sections.

2.2.1.1 Motion correction

Even small movements of the head have an influence of the signal quality in that they change information about spatial localization of cortical activity. Therefore, motion related variance also including movements that are related to physiological (cardiac and pulmonary) factors has to be corrected. The acquired functional volumes are aligned in space by rigid-body transformations, where the variance of the original position can be described by 6 motion parameters including linear and rotational transformation. Thereby the first image-time series serves as reference against all subsequent scans are aligned.

2.2.1.2 Normalization

Since there exist enormous differences between the images of individual brains, they have to be spatially (stereotactically) normalized into a standardized space in order to generalize individual results to a larger group. Almost all PET and fMRI studies report results in the Talairach coordinate system (Talairach and Tournoux, 1988).[1] In both the Talairach and the MNI system, all locations within a three-dimensional space of the brain are represented as coordinates. Positive and negative distances are relative to the intercommissural (AC-PC) line in the horizontal (x), anterior-posterior (y), and vertical (z) directions. The origin of this coordinate system (x=0, y=0, z=0) corresponds to the centre of a small brain region, the anterior comissure (AC). A three-number coordinate defines the spatial location of any point in the human brain with a negative x value pointing to left hemisphere location, and negative y value referring to a point posterior to AC, and a negative z value relating to a site inferior to the plane parallel to the AC-PC line. This coordinate system enables brain imagers to compare the locations of a particular activation of brain site among studies, conditions, and subjects.

[1] Alternatively some researchers prefer the template brain provided by the Montreal Neurological Institute (MNI; http://www.mni.mcgill.ca). In terms of size and extent these two coordinate systems are similar.

2.2.1.3 Spatial Smoothing

The purpose of spatial smoothing is to cope with functional anatomical variability that is not compensated by spatial normalization. Thereby, the acquired images are convolved with an isotropic Gaussian kernel to increase the signal to noise ratio and the statistical power. The Gaussian kernel is defined by its full width at half maximum (FWHM) and compensates for residual between-subjects variability after normalization.

2.2.1.4 Statistical analysis of fMRI data

In order to identify significant responses of certain regions of the brain that correlate with the stimulus presentation, it is necessary to apply statistical methods to the pre-processed data. There are several statistical approaches to quantify the correspondence between data and task paradigm. The so-called general linear model (GLM) is based on the concept that the data is a linear combination of model functions including noise. The correlation analysis compares the modelled time courses with the measured voxel time courses providing a correlation value r. Thereby r provides information about how strong these two time courses co-vary. The obtained statistical values of every voxel provide data for a statistical map, which will be presented at a given level (threshold). The statistical map can be visualized by coloured voxels representing values with a significant t- or p-effect.

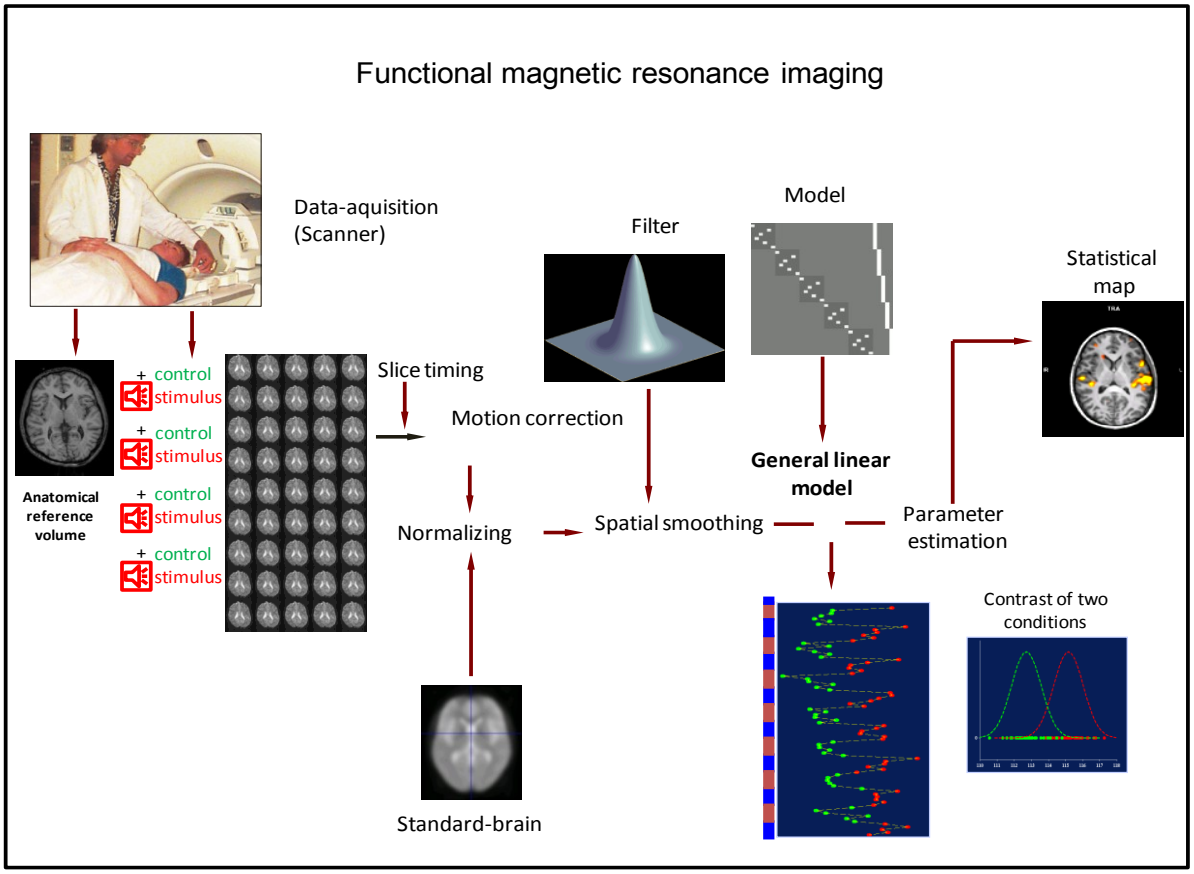


Fig. 12. The different processing steps in functional magnetic resonance imaging. Left: acquisition of anatomical and functional images during an auditory processing task (auditory stimulus presentation alternating with baseline/control condition). Middle: Pre-processing of the data. Right: Statistical analysis *(Figure adapted from Frackowiak et al., 1997)*

3 Own studies

Brain lesions in the language and motor network are one of the most common causes of chronic disability and have an impact on many activities of daily life. The language and motor studies that are presented in the following sections aimed at making a contribution to the ongoing debate how the brain masters damage in terms of plastic processes and how the observed reorganization pattern are related to the functional recovery. Although many studies investigated the cortical activation pattern and the corresponding functional recovery in patients with brain lesions, there is still a debate about whether improvement represents sparing or restoration of function in perilesional zones of the ipsilesional hemisphere or recruitment of homologous contralesional regions. Since these issues are still unclear in the field of language and motor functions, which share many aspects of functional reorganization, we were interested to learn more about language *and* motor reorganization to both compare and differentiate the two processes against each other. To consider aspects of individual variability and task dependent differences in the neural representation of language and motor processes, it is pivotal to previously assess the corresponding functions in healthy individuals. Therefore we conducted two studies (1, 3) where we investigated language and motor tasks in healthy subjects which were then assessed in patients with damage in the language (tumour and stroke, study 2) and sensorimotor network (study 4). Furthermore, the influence of additional therapeutical intervention (e.g. interactive cognitive therapy) on functional recovery and the corresponding activation pattern was assessed in patients from the acute state to a follow up period of three month (study 4). The main goal of the thesis was to gain insight into plastic processes following brain damage and to compare the reorganization of different functions and etiologies of brain lesions and its impact on recovery. The findings of these studies should provide a better understanding of the many neuronal pathways that are available to sustain each type of language and motor task. Furthermore it was aimed at assessing the influence of newly developed therapeutical interventions on the observed reorganization processes.

3.1 Study 1

Mapping of visual and auditory language processing by means of an fMRI protocol

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Abstract

A reliable identification of language-related areas in the presurgical benefit-risk evaluation of patients with brain tumors has become increasingly more relevant with the availability of non-invasive functional imaging techniques and the development of surgical navigation systems that allow the incorporation of functional information. The aim of this study was to establish an fMRI language protocol that identifies regions of the language system, which are essential for language processing. The protocol comprises two multimodal tasks known to assess different linguistic processing abilities. The *picture/word matching task* consisted of line drawings of common objects presented together with a printed or spoken word that was either the name of the depicted object or of a semantically related object. The *lexical decision task* consisted of written or spoken words or pronounceable non-words of one or two syllables' length. Accuracy of response and reaction times were measured. Overlapping responses in perisylvian areas were obtained across tasks and input modality, but there were also notable differences, pointing to an input specific and task dependent representation of language. The results demonstrate that the two language paradigms are most suitable for pre-surgical planning: The presentation of comparable sets of stimuli in two modalities results in a more comprehensive evaluation of language processing and the collected behavioral measures allow for a more reliable interpretation of the fMRI data. Furthermore, assessing language comprehension rather than language production minimizes motion artefacts and provides a more differentiated appraisal of language lateralization.

Introduction

The goal of neurosurgical resection in patients with disease processes such as brain tumours, vascular lesions, and epilepsy is maximal excision with minimal risk of inducing postoperative neurological deficits (Sunaert, 2006; Pouratian et al., 2002; Pelletier, et al., 2007; Tharin & Golby, 2007). Thus far, the intracarotid amobarbital or Wada test and intraoperative cortical stimulation have been considered the gold standard in assessing language dominance, particularly in patients about to undergo surgery for the removal of the epileptic focus (cf. Rausch, 1992). Reliable as these two language mapping techniques have proved to be their invasiveness is an additional risk for neurosurgical patients. Functional magnetic resonance imaging (fMRI) is a completely non-invasive procedure, and several studies in which fMRI activations in language paradigms were correlated with the results of the Wada test have shown that fMRI activation indices constitute a suitable tool for assessing language lateralization (Binder et al., 1996; Lehéricy et al, 2000; Rutten et al., 2002a; Woermann et al., 2003). Furthermore, with the Wada test examination time is limited and language dominance must be assessed within a short time frame; with fMRI procedure an activation paradigm can be repeated easily in a single session and on multiple occasions, providing information not

only about language lateralization, but also about the cortical areas involved in complex language processing.

A critical issue in fMRI-based assessments of language lateralization is the inter-individual variability of activation. Different factors may account for this variability. Considerable structural differences are found in regions subserving language functions; as demonstrated by Amunts and co-workers (2004) Broca's region, comprising Brodmann areas 44 and 45, displays high intersubject variability with respect to size and shape of these two areas and to their relationship to surrounding sulci. It has also been suggested that a relationship exists between the anatomical asymmetry of the planum temporale and hand preference, left-handers showing a smaller leftward asymmetry (Steinmetz et al., 1991; Foundas et al., 2002). A larger left planum temporale appears to be found with a more lateralized pattern of activation in language tasks, but handedness is not correlated with a language-related functional asymmetry (Josse et al., 2003; Tzourio et al., 1998). Although handedness does not predict functional variability it may influence the interhemispheric relationship during language processing (Tzourio-Mazoyer et al., 2004). A number of neuroimaging studies have reported gender differences, females displaying greater bihemispheric activation during language tasks than males (Pugh et al., 1996; Schlösser et al., 1998; Kansaku et al., 2000). However, there is also neuroimaging data arguing against substantive differences between men and women in the large-scale neural organization of language processes (Frost et al., 1999). Meta-analysis studies in which language-related activity was assessed with functional imaging techniques showed no significant difference in language lateralization between men and women at the population level, but reasoned that it might be observed with some language tasks (Sommer et al., 2004; for a discussion of the inconsistent findings see Harrington & Tomaszewski Farias, 2008). A further factor that may contribute to the variability of activation is the effect of aging upon the hemodynamic response measured by fMRI (Huettel et al., 2001). Higher levels of activation have been found in Broca's and Wernicke's area in younger compared to older individuals (Rotte, 2005), healthy older individuals often showing compensatory recruitment of novel brain regions when performing at the level of their younger adult counterparts (Wingfield & Grossman, 2006).

A major problem raised by the variability of activation with respect to presurgical planning is how to determine the areas that are truly relevant for the production and comprehension of both spoken and written language. Conjunction analysis has been proposed as an analysis approach to define the location of critical language areas in the normal brain. Listening to factual stories (comprehension task) and the covert generation of verbs semantically related to heard nouns (production task) were thus found to have a common network of activations that

included three left hemisphere areas known to elicit impairment in both language comprehension and production when involved by a lesion or electrically stimulated (Papathanassiou et al., 2000). The combined task analysis (CTA) used in some studies, conceptually similar to a conjunction analysis, is also geared toward identifying brain regions that are involved in generic language functions rather than regions that are involved in functions that are specific to a single task (Rutten et al., 2002; Jansen et al., 2006).

As pointed out by Seghier (2008) in his succinct review on methodological issues to be considered in studies concerned with language lateralization, task selection, input modality, and baseline condition can influence the hemispheric distribution of activated areas. Significant effects of the baseline condition on the hemispheric distribution of functional activation patterns was found in an fMRI-based study of language lateralization by Hund et al. (2001). The extent of activation and the amount of bilateral involvement observed in the two target tasks differed depending on baseline condition. When structural decision tasks served as baseline condition, data analysis showed mainly left-hemisphere activations. Another study by Price et al showed that fixation as baseline condition elicited an increased bilateral activation pattern (cf. Price et al., 2005). Only few studies have investigated the effects of input modality on the activation pattern of word processing. Both auditory and visual word presentation were found to activate inferior frontal cortex when volunteers were required to make semantic word class decisions (concrete/ abstract), left posterior temporal activations being more pronounced during auditory than visual word presentation (Chee et al., 1999). In an fMRI study aimed at uncovering the network of regions active during phonological word processing Burton et al. (2005) found strong increases in activity of the left posterior inferior frontal gyrus in the two phonological discrimination tasks across both modalities, with modality-specific activations observed in areas involved in sensory processing (i.e., the left superior temporal gyrus adjacent to or including auditory cortex in auditory tasks, and the lingual gyrus in visual tasks). Another significant point revealed by the study is that activation from auditory and visual stimulus presentation is modified by stimulus type and task demand. As also demonstrated by Heim et al. (2007) modality of word presentation does not appear to influence the involvement of BA 44 during lexical decision making.

Task selection has been guided by different methodological considerations. For an fMRI language protocol to be clinically useful it must give robust frontal and temporal language–related activity at the level of individuals. Word generation is a widely used task that has been found to be a reliable predictor of laterality, eliciting activity primarily in Broca's area. The subject is asked to produce, covertly or overtly, as many words as possible beginning with a given letter (e.g. "s" or "t", also known as letter fluency; Lurito et al. 2000; Baciu et al., 2005;

Jansen et al., 2006) or belonging to a specified semantic category (e.g. colors, tools, etc.; Stippich et al., 2003). In their seminal study of the cortical anatomy of single word processing Petersen et al. (1988) had subjects perform a verb generation task, i.e. to think of a verb semantically related to the presented noun (e.g. to say “eat” if the word “cake” is presented), the aim being to target areas involved in semantic processing. With both auditory and visual stimulus presentation this noun-verb association task activated a left inferior frontal area. Given that the task has been found to have a robust reproducibility it is frequently used in presurgical language mapping protocols. (Herholz et al. 1996; Benson et al., 1999; Ramsey et al., 2001; Rutten et al., 2002b; Burton et al. 2003; Otzenberger et al., 2005). However, as has been argued by Thompson-Schill et al. (1997, 1999) it is not retrieval of semantic knowledge *per se* that is associated with left inferior prefrontal cortex activity but rather the selection of relevant semantic knowledge from a set of competing alternatives (cf. Wagner et al., 2001; Noppeney et al., 2004; Snyder et al., 2007). To define more differentially the location of critical language areas it has been suggested that two tasks be used, each one addressing an inherent component of language, in particular phonological and semantic processing. In a number of studies a rhyme task was used to elicit the pattern of activation associated with phonological processing (Lurito et al., 2000; Billingsley et al., 20001; Seghier et al., 2004; Baciu et al., 2005; Cousin et al., 2007). Semantic processing has been examined with tasks requiring subjects to judge whether two words belong to the same semantic category (Billingsley et al., 2001; Seghier et al., 2004) or are semantically related (Fernández et al., 2001, 2003; Cousin et al., 2007). Semantic decision tasks have also been designed with single word presentation (Démonet et al., 1992; Binder et al., 1997; Poldrack et al., 1999). Such semantic categorization tasks have been shown to elicit activation in the left inferior prefrontal cortex (Binder et al., 1997; Poldrack et al., 1999; Devlin et al., 2003; Seghier et al., 2004; Cousin et al., 2007), it being a debated issue whether activation of the inferior prefrontal cortex reflects cognitive control rather than domain-specific semantic processing (Gold & Buckner, 2002, Snyder at al. 2007). Phonological processing as evidenced in rhyme judgment tasks preferentially evokes activity in posterior parts of the left inferior frontal gyrus and in the inferior parietal lobule (Burton et al., 2003; Cousin et al., 2007), with some reports of activation in the superior temporal gyrus (Lurito et al., 2000; Billingsley et al., 2001; Seghier et al., 2004). Word-finding difficulties are a common symptom of left hemisphere brain damage so that covert picture naming would seem to be a reasonable task to assess hemispheric language dominance (Benson et al., 1999; Rutten et al., 2002b; Harrington et al., 2006; Jansen et al., 2006). However, confrontation naming has been found to be less lateralized than verb generation. In their study of fMRI-based mapping of language Otzenberger et al (2005) had subjects perform three different tasks, each known to elicit left-lateralized activation in specific brain areas. A lexical decision task served to identify the area within the left posterior inferior

temporal cortex dedicated to reading. The task did not activate this area as consistently as it did the left inferior frontal cortex. This finding is likely to reflect the inconsistency in activation differences between reading words and pseudowords observed in occipito-temporal brain regions. In the neuroimaging literature there are some reports of words producing greater activation than pseudowords in the fusiform gyrus (Fiebach et al., 2002), in other studies increased activation for pseudowords relative to words was noted in the left posterior inferior temporal gyrus (Mechelli et al., 2003). The reported inconsistent but highly significant effects of word type at the individual subject level may result from effects due to experimental groups consisting of a small number of subjects. But with both visual and auditory stimulus presentation the processing of words and pseudowords unvaryingly elicits increased activation in the left inferior frontal cortex, pseudowords producing enhanced activation in a left fronto-insular region (Fiez et al., 1999; Hagoort et al., 1999; Fiebach et al, 2002, Mechelli et al., 2003). To account for this differential increase of activity it has been argued that lexical search in pseudowords is mediated more strongly by rule-based processes subserving grapheme-to-phoneme conversion, even when the task (lexical decision) does not require the activation of phonological codes for the actual pronunciation of words. General processes in decision making could be contributing to the differential activity in the left inferior frontal cortex for words and pseudowords. As demonstrated in an event-related fMRI study with auditory stimulus presentation, it was more difficult and took participants longer to reject an item as pseudoword than accepting an item as a real word (Xiao et al., 2005; cf. Heim et al., 2007).

Aim of present study

In recent years, especially with the implementation of sophisticated neuroimaging techniques, it has become quite evident that several regions outside the classical Broca and Wernicke language areas are engaged in the comprehension and production of language, i.e. that the brain's language map extends beyond the contributions made by Broca and Wernicke. This is not to say that the classical conceptualization of the neural basis of language is wrong but that it is anatomically quite underspecified (for a review, see Poeppel & Hickock, 2004). In developing a protocol for presurgical language mapping we adopted the neuroanatomic view of the functional architecture of language that has been advanced by Hickock and Poeppel (2000; 2004; see also Wise, 2003; Scott & Wise, 2004). Given the empirical evidence that the neural network supporting speech perception varies as a function of the task Hickock and Poeppel hypothesized that there are at least two distinct pathways that participate in speech perception in a task dependent manner. Drawing on knowledge gained in past years on the organization of vision these authors argued that a ventral pathway, projecting ventro-laterally toward inferior posterior temporal cortex, serves as an interface between sound-based representations of speech in the superior temporal gyrus and widely distributed conceptual

representations and is therefore involved in tasks that require access to the mental lexicon. The dorsal pathway, projecting dorso-posteriorly toward the parietal lobe and ultimately to frontal regions, is taken to play a greater role in tasks that require explicit access to sub-lexical speech segments, the inferior parietal lobe being part of an interface system that mediates between auditory and articulatory representations of speech. The two pathways are unlikely to be independent; as the aphasiology literature illustrates, impaired semantic processing is observed with left temporoparietal lesions. But as more recent brain stimulation studies appear to suggest, the semantic ventral stream could be constituted by at least two parallel pathways within the dominant temporal lobe, namely a direct pathway, the inferior occipitofrontal fasciculus connecting the posterior temporal areas and the orbitofrontal region, and an indirect pathway subserved by the inferior longitudinal fasciculus (Mandonnet et al., 2007).

Word retrieval, common to speech perception and speech production, is generally viewed as involving processes that are devoted to accessing both the meaning of a word (lexical semantics) and its sound structure (lexical phonology). In terms of Hickock and Poeppel's proposed functional neuroanatomic framework the processing of word meaning and phonetic/ phonological structure is subserved by distinct neural networks. Impaired word retrieval may be attributable to impairment at the level or site of processing that allows access to phonological word forms, at the level of lexical-semantics, or in linking word forms to lexical-semantic representations. For example, after focal brain damage the ability to retrieve either the phonological or the orthographic word form may be impaired while word comprehension is intact. A task such as picture naming pivots on word retrieval. Functional imaging studies of picture naming have shown widespread activation of left perisylvian and extrasylvian cortex (Hirsch et al., 2001, Abrahams et al., 2003; Indefrey & Levelt, 2004; Kemeny et al., 2006). Thus it is rather likely that depending on site of lesion different components of the naming process will be disrupted, but all resulting in impaired naming (DeLeon et al., 2007). To avoid motion artefacts we used a *picture-word matching* task rather than confrontation naming to assess lexical processing. Such a task also involves the ability to access both word meaning and word form.

Lexical decision tasks, requiring subjects to judge whether a written or spoken stimulus item is a real word or a pronounceable but meaningless non-word, have been widely used to study various aspects of visual and auditory word recognition, e.g. effects of word length, frequency, and familiarity, the cortical organization of the mental lexicon, or as an index of impairment following brain damage (for a review, see Goldinger, 1996). But contrary to picture-word matching or confrontation naming they do not necessitate an exhaustive lexical search; the mere presence of words and pseudowords has been shown to implicitly activate language-related regions in the left hemisphere, comprising not only the classic perisylvian areas but

also areas in left inferior and middle temporal cortex, inferior parietal lobe, prefrontal cortex (Price et al., 1996). We hypothesized that a lexical decision task might activate preferentially left hemisphere cortical areas sensitive to phonological processing, involving the dorsal stream. And we expected the picture word-matching task to activate more strongly the neural network devoted to lexical-semantic processing, involving left posterior inferotemporal cortex, the left superior temporal cortex, and the inferior frontal cortex (Graves et al., 2007).

Materials and Methods

Subjects: Sixteen healthy, native speaking German subjects (age range 23-37) were recruited for this study (nine females, seven males). All subjects had normal or to normal corrected eye-sight and normal hearing. A hand dominance inventory (Oldfield, 1971) revealed strong right-hand dominance. None of the subjects had any history of a neurological disorder. All participants gave their written consent, and the study was approved by the local ethics committee.

Stimuli

The study comprised two tasks that engage different linguistic processing abilities. Stimuli were presented in either the auditory and visual mode. The *picture/word matching task* consisted of line drawings of common objects together with the presentation of the printed or spoken word that was either the name of the object or the name of a semantically related object. The visual control task consisted of pairs of random line drawings, taken from Kimura's Recurring Figures Test. There were 60 stimulus items in each of these three conditions. With auditory word presentation rest was used as baseline. The *lexical decision task* consisted of written or spoken one- or two-syllable words or pronounceable non-words. The visual control task comprised visually presented consonant strings with or without a "T" (letter detection). Each of the three conditions comprised 90 stimulus items. Again, rest served as baseline with auditory word presentation.

Experimental Procedure

Prior to scanning participants were informed about the experimental procedure. During scanning, subjects lay in a supine position and viewed the stimuli, which were back-projected onto a translucent screen, by means of a mirror mounted on the head coil. For the binaural stimulus presentation, we used an MR-compatible piezoelectric auditory stimulation system incorporated into standard Philips headphones. In the picture-word matching task (Fig. 1), subjects had to decide whether the picture matched the word or whether the two line drawings (control task) were the same or not by pressing the corresponding button with the right index finger. In the lexical decision task (Fig. 2), participants had to decide whether the stimulus item

was a word or a non-word or whether the consonant strings contained a T with a yes or no button-press. All stimuli were presented for 2 s. During the rest condition, subjects had to fixate a small cross displayed in the middle of the screen to prevent eye-movements.

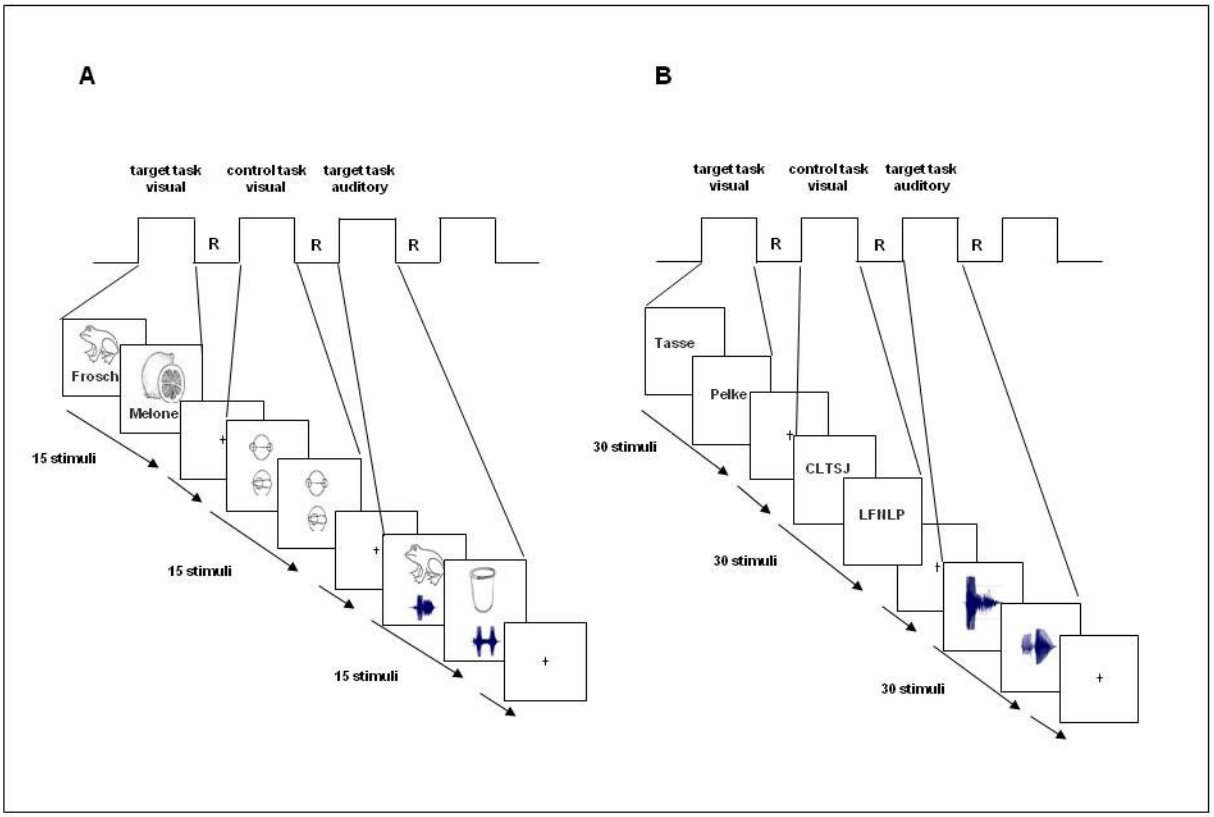

Fig. 1. Design of the word-picture matching (A) and the lexical decision task (B) with an example of each task/condition block.
A. In the visual target task, a printed word is presented below a picture, in the auditory target task a spoken word is presented with a picture. In both tasks a decision must be made as to whether the picture matches the presented word. In the visual control task the identity of the two figures must be judged.
B. In the visual target task, a printed word (Tasse) or pseudoword (Pelke) is presented, in the auditory target task words and pseudowords are presented via headphones during the presentation of a crosshair. In both tasks the lexical decision, the subject has to decide whether the presented word is a common German noun with a yes or no answer. In the visual control task, a decision must be made as to whether the consonant-string contains the letter T. Target and control tasks are separated by a 15s rest condition (R) in which a crosshair must be fixated.

For the two tasks we used a block design with the three task conditions (target task visual modality, target task auditory modality, control condition) presented pseudo-randomly. The picture-word matching task consisted of 30s periods of stimulus presentation alternating with 15s periods of rest (5 repetitions). The lexical decision task consisted of 60s periods of stimulus presentation alternating with 15s periods of rest (3 repetitions). Total scanning time was 540s for the picture-word matching task and 660s for the lexical decision task. During data acquisition accuracy of responses and reaction times were recorded to assess the behavioral performance of the subjects. Presentation of the stimuli and recording of behavioral

responses was done with *Presentation* (http://www.neurobs.com/). The left arm was positioned along the body.

Acquisition and analysis

MRI was performed in a 3.0 T MR system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an 8 channel SENSE™ head coil. For functional imaging a T2* weighted, single-shot, fast field echo, EPI sequence of the whole brain (TR = 3000ms, TE = 40ms, flip angle = 82°, FOV = 220mm × 220mm, acquisition matrix = 128 × 128, in plane resolution = 1.7mm × 1.7mm, slice thickness = 3mm, slice gap = 0, slices = 39) with a SENSE factor 2 was used (Pruessmann et al., 1999). Anatomical reference images of the whole brain were acquired at the end of the imaging session using a 3D, T1-weighted, field echo sequence (TR = 20ms, TE = 2.3ms, flip angle = 20°, in plane resolution = 0.9mm × 0.9mm, slice thickness = 0.75mm, 210 slices). These slices were transformed to iso-voxel size (1mm × 1mm × 1mm), and to Talairach space (Talairach & Tournoux, 1988).

Post-processing and data analysis was performed with the Brain Voyager QX 1.8 software package (Brain Innovation, Maastricht, The Netherlands). To remove unwanted signal components, data pre-processing was done for each subject prior to the computation of group analyses. Thereby, the standard parameters implemented in BrainVoyager QX 1.8 were adopted to diminish arbitrary selection of pre-processing parameters. Images were 3D motion corrected by means of trilinear interpolation. Spatial smoothing was performed by applying a Gaussian filter of 4mm FWHM, to allow for the integration of signals in an area of less than a centimetre. Within this range, smoothing merely reduces the noise by simultaneously enhancing the signal. Temporal smoothing included linear trend removal and high pass filter (limited to three cycles). Prior to group analysis, functional volumes were automatically co-registered to the individual three-dimensional structural scans and transformed into Talairach space (Talairach & Tournoux, 1988).

fMRI Analysis

For the single subject analysis the stimulation condition was modelled using a general linear model (GLM) convolved with the standard two gamma haemodynamic response functions resulting in t-contrast maps corrected for multiple comparisons with q(FDR) ≤ 0.01 showing the contrasts target versus rest (auditory modality). The contrasts target versus control condition (visual modality) was performed with t = 4 uncorrected. FDR (false discovery rate) is a recent development in statistical hypothesis testing to control the type I error (rejection of a true null hypothesis). FDR has a higher power than Bonferroni correction as the threshold varies automatically across subjects with consequent gain in sensitivity. The parameter q has

the advantageous feature of being comparable across studies. The correction accounts for cluster size, i.e. the bigger the cluster the more unlikely are non-random activations hence a lesser correction is accounted for (Genovese et al., 2002).

For the group, a two-step analysis was performed on the basis of the linear model. A random effect analysis was performed using the multi-study option of the analysis software to detect the brain regions involved in the picture-word matching and lexical decision task. For both tasks, comparison of target versus control condition (visual modality $t = 4$, uncorrected) or rest (auditory modality, $qFDR \leq 0.05$ corrected) were performed.

Results

Behavioural data

Statistical analyses were conducted to determine whether there were differences in performance between stimulus modality in each of the two tasks. To this end, t-tests were performed on accuracy and reaction time data, separately for the two tasks. In the picture-word matching task no statistically significant difference was found between the two presentation modes with respect to response accuracy ($t(15) = 0.718$; $p = 0.491$) and reaction time ($t(15) = 0.954$; $p = 0.365$). In the lexical decision task visual stimulus presentation resulted in significantly more correct responses ($t(15) = 3.331$; $p = 0.009$) and shorter reaction times ($t(15) = 3.386$; $p = 0.008$). Significantly more correct responses were achieved in judging the similarity of random figure pairs, both with word presentation in the visual ($t(15) = 6.713$; $p = 0.000$) and auditory ($t(15) = 4.061$; $p = 0.003$) word presentation. However, comparing reaction times to similarity judgments with auditory and visual picture-word matching did not reveal any significant differences ($t(15) = 1.572$; $p = 0.150$ and ($t(15) = 0.671$; $p = 0.519$, respectively). Significant differences in reaction times were obtained when comparing letter detection with lexical decision in the auditory ($t(15) = 5.369$; $p = 0.000$) and visual mode ($t(15) = 4.101$; $p = 0.003$). Noteworthy is the finding that accuracy of response in letter detection and visual lexical decision did not differ ($t(15)$ 1.821; $p = 0.102$).

	picture-word matching	lexical decision
auditory presentation	0.91 (0.06)	0.86 (0.07)
visual presentation	0.88 (0.08)	0.93 (0.08)
random figures (visual control condition)	0.97 (0.05)	
letter detection (visual control condition)		0.98 (0.3)

Tab. 1. Mean percent correct as a function stimulus modality (standard deviation in parentheses)

	picture-word matching	lexical decision
auditory presentation	1143 (150)	1120 (86)
visual presentation	1074 (278)	963 (160)
random figures (visual control condition)	1022 (236)	
letter detection (visual control condition)		838 (176)

Tab. 2. Mean reaction time (ms) as a function of stimulus modality (standard deviation in parenthesis)

Functional imaging data across subjects

Visual picture-word matching versus comparison of random line drawings

An extended network of both peri- and extrasylvian areas was found activated when comparing visual picture-word matching to similarity judgments of random line drawings. The distributed network of activation primarily involved the left hemisphere, namely the supplementary motor area, the premotor area, the inferior frontal gyrus (pars triangularis), the anterior insula, the superior temporal gyrus, and the inferior occipital cortex. Bilateral activation was observed in the middle temporal gyrus and the fusiform gyrus (Table 1; Fig. 4).

Auditory picture-word matching versus

The auditory picture-word matching task compared to rest also revealed increased neuronal responses in an extended network of both peri- and extrasylvian areas, but in contrast to visual word-picture matching relative to similarity judgments of random line drawings the distributed network of activation was bilateral. It included the inferior frontal gyrus (pars opercularis), anterior insula, the superior temporal cortex, together with the middle temporal gyrus, the fusiform gyrus, inferior parietal cortex and occipital cortex; in addition, activation increases were noted in the left sensorimotor cortex, the right supplementary motor area and the right premotor cortex (Table 1; Fig. 4).

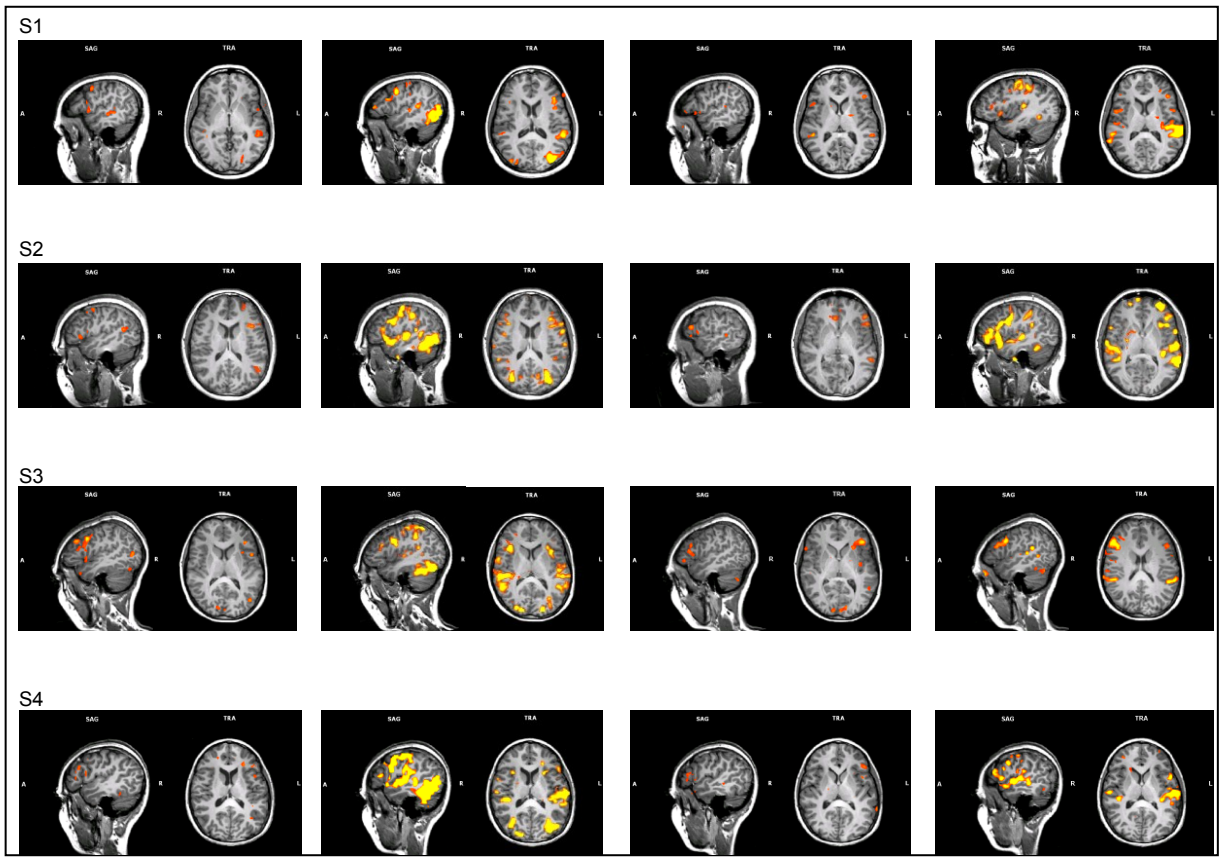

Fig 4. Activation maps of 4 representative subjects with the contrasts: For both tasks comparison of target versus control condition (visual modality t ≤ 4, uncorrected) or rest (auditory modality, qFDR≤ 0.05 corrected). Abbr.: VPWM: visual picture-word matching, APWM: auditory picture-word matching, VLD: visual lexical decision, ALD: auditory lexical decision, cons.string: consonant-string.

Table 1: Picture-word matching

Comparison of visual word-picture-matching and random figure matching

	Left hemisphere					Right hemisphere				
Location	k	Mean T value	x	y	z	k	T value	x	y	z
SMA	187	4.57	-4	8	48					
PM	242	4.29	-40	-2	48					
IFS	1711	4.98	-42	-10	31	-	-	-	-	-
IFG (tri)	351	4.5	-44	27	14	-	-	-	-	-
Anterior insula	73	4.64	-26	24	7					
Superior temporal	6	4.15	-51	-39	7					
Mid temporal	133	4.53	-57	-36	4	71	4.4	42	-62	11
Fusiform gyrus	9208	5.52	-29	-54	-15	3473	4.87	22	-64	-12
Inferior occipital	186	4.27	-31	-73	24		-	-	-	-

Comparison of auditory word-picture matching and rest

	Left hemisphere					Right hemisphere				
Location	k	T value	x	y	z	k	T value	x	y	z
SMA						4537	6.06	1	1	48
premotor						3874	5.75	48	3	33
S1	6350	6.28	-43	-26	48					
M1	2307	5.66	-33	-11	47					
IFG (op)	390	5.3	-38	12	6	248	4.96	49	10	0
Rolandic operculum	50	5.55	-48	3	5					
Anterior insula	652	5.51	-29	20	8	368	4.91	34	20	6
STL	9729	6.21	-53	-24	8	9776	6.34	54	-21	5
Mid temporal	1109	5.58	-45	-48	4	337	5.43	53	-41	6
Fusiform gyrus	16074	7.46	-37	-54	-13	15988	8.17	36	-54	-14
Inferior parietal	6820	5.93	-35	-42	43	1069	5.24	41	-36	39
Occipital superior	1711	5.82	-27	-61	43	2078	5.32	28	-54	41

Table 1. Mean t-values, coordinates of the centres of gravity (Talairach and Tournoux, 1988), and volumes of activated tissue of the regions with significant activation for the contrasts visual word-picture-matching and random figure matching (t = 4, uncorrected) and auditory word-picture matching and rest (qFDR≤ 0.05 corrected)

Visual lexical decision task versus visual letter detection task

The contrast between lexical decision with visual stimulus presentation and letter detection in written consonant strings revealed three left lateralized foci of activation in the pars triangularis of the inferior frontal gyrus and one in the pars opercularis. Further left lateralized increases of activation were found in the anterior insula, the middle temporal gyrus, the fusiform gyrus, and the supplementary motor area (Table 2; Fig. 4).

Auditory lexical decision task versus rest

Lexical decision with auditory stimulus presentation relative to rest elicited a predominantly bilateral pattern of activation in the anterior insula, the pars opercularis of the inferior frontal gyrus, the superior temporal cortex, and the parietal cortex. Stronger hemodynamic responses were observed in the left pars triangularis of the inferior frontal gyrus and in the Rolandic operculum as well as in primary sensory cortex. The activation in the supplementary motor area and premotor cortex was also bilateral, but more pronounced in the right hemisphere, neuronal activity in the primary motor cortex being more left-lateralized (Table 2; Fig. 4).

Table 2: Lexical decision task

Comparison of visual lexical decision task and consonant letter detection

	Left hemisphere					Right hemisphere				
Location	k	T value	x	y	z	k	T value	x	y	z
SMA	205	4.56	-4	1	55	-	-	-	-	-
Pre-SMA	172	4.26	0	16	46	-	-	-	-	-
IFG (tri)	599	4.48	-46	28	10					
IFG (tri)	622	4.85	-42	14	23					
IFG (tri)	66	4.48	-42	36	4					
IFG (op)	588	4.95	-46	16	5		-	-	-	-
Anterior insula	102	4.51	-29	19	6	-	-	-	-	-
Superior temporal	399	4.55	-56	-38	4					
Fusiform gyrus	21	4.34	-36	-39	-19					

Comparison of auditory lexical decision task and rest

	Left hemisphere					Right hemisphere				
Location	k	T value	x	y	z	k	T value	x	y	z
SMA						2503	4.85	1	-1	53
Premotor	129	4.22	-45	-6	46	1311	4.63	47	8	25
Postcentral S1	141	4.4	-56	-22	40					
M1	172	4.33	-32	-13	56	634	4.68	50	-2	38
IFG (op)	623	4.91	-48	10	4	460	4.5	49	13	4
IFG (tri)	41	4.18	-40	24	9	-	-	-	-	-
Anterior insula	61	4.23	-32	22	12	736	4.67	35	21	7
Rolandic operculum	141	4.6	-51	7	4					
Superior temporal cortex	11730	5.69	-52	-22	8	10103	5.56	54	-17	3
Inferior parietal	121	4.2	-42	-41	49	44	4.33	43	-39	39

Table 2: Mean t-values, coordinates of the centres of gravity (Talairach and Tournoux, 1988), and volumes of activated tissue of the regions with significant activation for the contrasts visual lexical decision task and consonant letter detection (t = 4, uncorrected) and auditory lexical decision task and rest (qFDR≤ 0.05 corrected).

Discussion

In this study, we used two language tasks in order to identify the distributed neuronal networks involved in visual and auditory word retrieval, with the aim of providing sound evidence that the two tasks qualify as fMRI protocol for presurgical language mapping. In the picture-word matching task no statistically significant difference was found between the two presentation modes with respect to response accuracy and reaction time. Significantly more correct responses were achieved in judging the similarity of random figure pairs, both with word presentation in the visual and auditory word presentation. However, comparing reaction times to similarity judgments with auditory and visual picture-word matching did not reveal any significant differences. When comparing letter detection with lexical decision in the auditory and visual mode, significant differences in reaction times were obtained, whereas accuracy of response in letter detection and visual lexical decision does not differ. Both the picture-word matching task and the lexical decision task elicited left lateralized activation in the perisylvian cortex and in portions of parieto-occipito-temporal and frontal cortex as a function of task and presentation mode, the patterns of activation in line with the neuroimaging literature on word processing (for a review, see Price, 2000; Démonet et al., 2005). Auditory stimulus presentation resulted in a bilateral pattern of activation, in agreement with the view that speech perception is mediated bilaterally (Hickock & Poeppel, 2004; 2007).

Overall effects of task

The picture-word matching task was focused on the semantic processing of written and spoken words. With both modes of stimulus presentation bilateral activation was found in the medial fusiform gyrus (BA 19/37) and posterior parts of the middle temporal gyrus (BA 22/39). This bilateral inferior temporal activation may be related to the fact that subjects had to identify a depicted object, irrespective of whether the presented word was written or spoken. More importantly, the inferior temporal cortex has been shown in electrophysiological, clinical neuropsychological, and functional imaging studies to be involved in the processing of word meaning. Electrostimulation of the fusiform gyrus (e.g. during epilepsy surgery or via implanted subdural grids) has been reported to produce anomia (Lüders et al., 1991). Intracranial recordings of event-related potentials revealed the left anterior fusiform gyrus to be sensitive to the semantic content of letter strings (Nobre et al., 1994). Naming disturbances with relatively intact comprehension have been described in patients with circumscribed lesions of the posterior middle and inferior temporal gyri (Raymer et al., 1997; Foundas et al., 1998). Functional imaging studies have also demonstrated the involvement of the inferior temporal cortex in language processing. In a semantic decision task on heard word triplets activation was observed bilaterally in the anterior fusiform gyrus, activity within the right anterior fusiform gyrus correlating positively with the accuracy of semantic decisions (Sharp et

al., 2004). The occurrence of auditory activations in inferiotemporal cortex appears to be task dependent as argued by Cohen et al. (2004); there is converging evidence that subcomponents of the inferotemporal cortex are multimodal and engaged in phonological auditory processing (Benson et al., 2001; Booth et al., 2002).

Written word presentation evoked left lateralized neuronal responses in posterior superior temporal cortex (BA 21/22), the anterior insula, and in the pars triangularis (BA 45). It is a pattern of activation that has been associated with semantic retrieval and semantic judgement tasks (Friederici et al., 2000; Noppeney et al., 2004), with the left inferior prefrontal cortex hypothesized to guide controlled semantic retrieval (Wagner et al., 2001). Of particular interest with respect to the task as a tool in presurgical language mapping are the descriptions of a ventral semantic stream connecting the posterior temporal regions and the inferior frontal cortex/ dorsolateral prefrontal cortex via the inferior occipito-frontal fasciculus. With the aim of gaining insight into the anatomo-functional connectivity underlying the cortical network implicated in semantic processing Duffau et al. (2005) compared the anatomical locations of the sites where semantic errors were elicited by cortico-subcortical electrostimulation of this fiber bundle in patients undergoing surgery for a low-grade glioma in the dominant hemisphere with pre- and post-operative DTI (diffusion tensor imaging), a technique that enables fiber tracking. The result of their validated comparative study has shown that the resection cavity on the post-operative MRI with DTI touched the fiber tract in agreement with the intraoperative subcortical stimulation findings (Lehéricy et al., 2007).

Auditory word presentation resulted in a bilateral activation pattern involving the posterior superior temporal gyrus (BA 41/ 42), the supramarginal gyrus (BA 40), the anterior insula, and the pars opercularis in the inferior frontal cortex. These structures have been implicated in the sensory perception and phonetic identification of spoken word forms, phoneme processing, and lexical-semantic retrieval (for a review, see Binder & Price, 2001). Again, based on the functional findings of intraoperative electrostimulation and tractography studies (Catani et al., 2002) Duffau and collaborators have hypothesized the existence of a dorsal phonological processing stream, connecting the inferior frontal cortex/ventral premotor cortex (Duffau et al., 2003a) and the supramarginal gyrus/posterior superior temporal cortex, via the arcuate fasciculus (Duffau et al., 2002) and cortico-cortical connections (Duffau et al., 2003b). As demonstrated by Catani et al. (2005) the frontal and temporal perisylvian language regions are connected through two parallel pathways, a direct pathway that is constituted by the long segment of the arcuate fasciculus connecting frontal and temporal lobes medially and an indirect pathway connecting temporal with parietal (posterior segment of the arcuate fasciculus) and parietal with frontal regions (anterior segment of the arcuate fasciculus).

Evidence from patients with aphasic disconnection syndromes appears to suggest that the indirect pathway relates to semantically based language functions (such as auditory comprehension and vocalization of semantic content), the direct pathway to phonologically based language functions (such as repetition).

Lexical decision tasks are essentially aimed at elucidating the processes involved in word recognition; unlike picture naming or rhyme judgment tasks they do not call for higher-level semantic or phonological processing. The lexical decision paradigm is commonly used in studies examining dual-route models of visual word recognition which postulate separate lexical (whole-word) and non-lexical (rule-based) mechanisms for accessing phonology. With vocabulary items (real words with or without regular print-to-sound correspondences) the phonological form can be "addressed" directly on the basis of the visual word form; with pseudowords (nonwords) the phonological form must be assembled by grapheme-to-phoneme rules. The evidence from functional neuroimaging for distinct areas of activation by words relative to nonwords has been rather unequivocal (Mechelli et al., 2003). It is also a debated issue whether the naming of vocabulary items, irrespective of their print-to-sound regularity, is semantically-mediated (Binder et al., 2005). We included a lexical decision task in our fMRI language mapping protocol as a tool to assess the network involved in lexical access. Again, auditory stimulus presentation elicited activations bilaterally in superior temporal cortex (BA 41/42) and ventral parts of the supramarginal gyrus (BA 40). And as in the picture-word matching task we found increased neuronal responses in inferotemporal cortex (BA 37) and posterior parts of the middle temporal gyrus (BA 21/22), however left lateralized and only with visual stimulus presentation. A set of frontal brain areas were activated, left inferofrontal areas (BA 44/45) showing activation increases with visual stimulus presentation, areas in dorsolateral frontal cortex (BA 44/6) with auditory stimulus presentation. It may be speculated that decisions were semantically mediated in the visual mode and phonologically mediated in the auditory mode (Fiez, 1997; Gold et al., 2005). For such an account of the differential pattern of activation it is perhaps not irrelevant that activation was bilateral in the auditory mode, left lateralized in the visual mode. In both tasks we found neuronal responses in the secondary motor cortex (SMA) and superior parts of the precentral gyrus (BA 6), left lateralized in the visual mode, right lateralized in the auditory mode. These areas are recruited in attention demanding tasks and are less related to language processing per se.

Overall effects of modality

In both tasks auditory word presentation induced activation increases bilaterally in superior temporal cortex and ventral parts of the supramarginal gyrus, regions of auditory preference involved in the processing of speech and short-term verbal store (cf. Jonides et al., 1998),

With the semantically based processing demands of the picture-word matching task we observed an increase of activation in insular/ inferior frontal cortex, cortical structures associated with the indirect pathway of connectivity between frontal and temporal language regions.

In conclusion, our fMRI language mapping protocol has been shown to be a robust but also sensitive tool for the lateralization and localization of relevant language networks. The recording of behavioural performance allows for a more reliable interpretation of the obtained activation pattern and thus extends the clinical applicability of the fMRI data. Our clinical fMRI protocol reveals activation in core language areas during both visual and auditory stimulus presentation in the two modalities and distinct modality specific brain responses. To obtain a more comprehensive picture of complex language processing, it is essential to use multimodal language paradigms, which also offer the possibility of assessing patients who fail to perform the task in one modality. Further validation of multimodal comprehensive language protocols will make fMRI an indispensable tool in the clinical setting.

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3.2 Study 2

Mapping of brain plasticity in stroke and tumour patients

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Abstract

In this fMRI study, we aimed at investigating cerebral plasticity and the corresponding language recovery in patients with vascular brain lesions in the chronic stage and patients with brain tumours before and after surgical intervention. The recovery patterns of language functions were investigated with two language tasks, previously assessed in healthy subjects (Keisker et al. in prep). The *picture/word matching task* consisted of line drawings of common objects together with a presentation of a printed or spoken word that was either the name of the object or the name of a semantically related object. The control task consisted of pairs of random line drawings, taken from Kimura's Recurring Figures Test. The *lexical decision task* consisted of written or spoken one or two syllable words or pronounceable non-words. The control task comprised consonant strings with or without a "T". Accuracy of response and reaction times were measured. The converging results show that reorganization patterns in stroke and tumour patients often include perilesional and right hemispheric language related areas with however different levels of effective functional recovery. Behavioural performance ranged from very successful and comparable to healthy subjects to very poor. The various behavioural deficits were dependent on the task itself (picture-word matching versus lexical decision), parts of the task demands (e.g. matching versus non-matching picture and word), input modality, and lesion site. There was no apparent difference in the reorganization pattern between stroke and tumour patients in terms of reorganization patterns and the corresponding functional recovery. Effective integration of right hemispheric language related areas was observed in the two groups, although there was a tendency for better behavioural performance in tumour patients.

Introduction

The human brain has the potential to reshape itself following injury. Functional recovery after focal brain lesions depends on the adaptive plasticity of the cerebral cortex and of the non-affected elements of the functional network (Heiss and Thiel 2006). Thereby, the progress of cerebral damage (fast in acute brain lesion and slow in tumours) may influence the pattern of reorganization and the corresponding functional recovery, e.g better functional compensation with slowly growing tumours compared to recovery following acute brain lesions (Duffau 2008). Hence we do a systematic comparison of the reorganization pattern of tumour and stroke patients and their corresponding behavioural performance.

Recovery of poststroke aphasia

The cerebral reorganization of language networks after stroke continues to be a matter of debate. The crucial issue remains whether language improvement represents sparing or restoration of function in perilesional zones of the left hemisphere or recruitment of

homologous right hemisphere regions. There are several studies which support the (transient) involvement of the non-dominant right hemisphere in recovering language processing (Raboyeau. et al. 2008; Richter et al. 2008; Saur et al. 2006; Cao et al. 1999; Price and Crinion 2005; Liégeois et al. 2004; Hillis and Heidler 2002; Klein et al. 2002; Romero et al. 2002; Calvert et al. 2000, Heiss et al. 1999; Thurlborn et al. 1999; Warburton et al. 1999; Karbe et al. 1998; Weiller et al. 1995) whereas other studies suggest recruitment of perilesional areas during language processing as been being most efficient in regaining language (Spironelli et al. 2008, Meinzer et al. 2008; Heiss and Thiel 2006, Rosen et al. 2000; Zahn 2002; Karbe et al 1998). In their longitudinal study assessing aphasic patients with an auditory comprehension task, Saur et al. (2006) found three consecutive phases of recovery correlating with improved language function: a strongly reduced activation pattern of remaining left language areas in the acute phase followed by an additional recruitment of homologous language areas and finally a return to a predominant left hemisphere activation in the chronic phase.

The role of the contralesional hemisphere for recovery remains controversial. It has been suggested that right hemispheric recruitment may reflect reliance on additional cognitive and linguistic resources which are not required by normal subjects during linguistic processes (Cappa 2000). There is also a debate whether this right sided language activity is because of a greater right hemispheric language function before the onset of the brain lesion or whether it is caused by the brain lesion itself. The latter case has been interpreted as phenomenon of transcallosal disinhibition probably reflecting less recovery than anomalous response caused by damage to the left hemisphere (Winhuisen et al. 2007; Price and Crinion 2005). However, there are studies that report right-hemispheric integration associated with improved language function in the acute and chronic state and before intensive therapeutical intervention within the chronic state (Winhuisen et al. 2005; 2007 Richter et al. 2008). The contribution of the right inferior frontal gyrus (IFG) to language recovery was investigated by Winhuisen et al. (2007) with repetitive transcranial magnetic stimulation (rTMS) applied over the left and right IFG. RTMS adversely affected language function in all patients at both time points when applied over the left IFG, and in some of the patients over the right IFG. This suggests that the left IFG supports the verb generation task whereas the right IFG probably does not take over the function of the left IFG after stroke, but helps support the left language function (see also Crinion and Leff 2007). These findings support the hierarchical model of functional compensation following vascular brain damage as suggested by Duffau 2008, implying a recruitment of ipsilesional (especially peri-lesional) areas before the recruitment of contralateral homologous regions.

Functional organization induced by tumours

In contrast to acute brain lesions that cause damage to the brain within the time range of hours or days having a fundamentally negative impact on language function, tumour growth is slow and allows a progressive redistribution of eloquent sites and is therefore often not noticed over years. Only extensive neuropsychological assessments reveal slight cognitive disorders and more often epileptic seizures point to the existence of the place occupying lesion (Duffau 2008). There are different patterns of reorganization of the language networks during tumour growth. Either the function persists within the tumour or eloquent areas are redistributed perilesionally around the tumour. Another pattern is the recruitment of a widely distributed network within the lesioned hemisphere or the compensation by homologous language related areas. The latter compensatory strategy seems to be more effective in patients who experience language impairment developed over a longer time period (Duffau 2008; Winhuisen et al. 2007; Thiel et al. 2005,2006) Finally, the combination of different patterns e.g. perilesional and contralateral reorganization of the language network can be observed (Duffau 2008). In order to identify factors which determine the transfer of language function to the right hemisphere in patients with slowly growing left lateralized tumours, Thiel et al. (2006) assessed healthy and lesioned patients with PET and TMS during the performance of a verb generation task. Only patients with slowly progressing tumours recovered right-sided language function as detected by TMS. In patients with rapidly progressive lesions no right-sided language function was found and language performance was linearly correlated with the lateralization of language related brain activation to the left hemisphere. The authors concluded that time is the factor which determines successful integration of the right hemisphere into the language network for compensation of lost left hemisphere language function in that slowly progressive brain damage and long disease duration allows the shift of language function to homologues areas.

Functional reorganization induced by tumour resection

In contrast to post-stroke reorganization of language functions which have been investigated during the last 50 years, the processes of post-resection recovery with tumours have emerged only recently as major subject of research (Duffau 2008). After resection of brain tumours in functional relevant areas Duffau et al. (2003) report immediate post-operative deficits and recovery within 3 months in tumour patients without neurological deficits presurgically. Thereby similar combinations of local and remote reorganizations were found, namely the recruitment of areas adjacent to the surgical cavity, recruitment of regions within the left dominant hemisphere and the contralateral non-dominant hemisphere. The case of normalized altered activation pattern and restoration of left-hemispheric dominance has also been reported (Heiss et al. 2003).

To further elaborate these findings and the corresponding models of reorganization, the present paper aims at investigating cerebral plasticity with functional magnetic resonance imaging (fMRI) in stroke and tumour patients with lesions of the language network and the corresponding behavioural recovery. Patients with vascular brain lesions in the chronic stage and patients with brain tumours before and after surgical intervention performed two language task that have previously been assessed with healthy subjects (Keisker et al. in prep.). Thereby the main questions were: How is the cortical activation pattern related to the observed behavioural performance and are plastic compensation processes different in patients with stroke compared to those with brain tumours? Our hypothesis was that the compensatory strategy of right-hemispheric integration is more often associated with improved language function in tumour patients, because the slowly growing tumour probably allows a shift of language functions to homologues sites on the right hemisphere.

Methods

Patients (Table 1)

5 patients with a space occupying lesion (glioblastoma, astrocytoma) in the left fronto-temporo-parietal language related network.

5 stroke patients with varying time (5-84 months) since onset and lesions (fronto-tempo-parietal language related network).

Age	Hand.	Pat	Aetiology	Site ol Lesion	Cognitive Disorder
33	L	CC (1)	stroke	Left insula, left superior temporal gyrus; left temporo-frontal area involving the operculum	Initially moderately impaired comprehension; written confrontation naming mildly impaired, oral confrontation naming severely impaired; good figural learning, recall, and recognition performance. good improvement of language functions in the months following stroke; persistent working memory deficits and reduced verbal span (3 years post onset)
49	R	HV (2)	stroke	Basal ganglia, insula, superior +medial temporal gyrus (left hemisphere)	initially severe global aphasia; persistent severely impaired oral language production (6 years post onset)
40	R	DD (3)	stroke	left temporo-parietal junction	initially moderate word-finding difficulties and comprehension deficits in both modalities; severely impaired repetition characterized by the symptoms of conduction aphasia; moderate impairments of executive functions; mildly impaired figural learning, recall and recognition performance (5 mths post onset)
45	R	RL (4)	tumour	Posterior region of the left temporal lobe	moderate word-finding difficulties; mild deficits in written and auditory comprehension tasks, no signs of reading, writing and calculation disorders, moderate impairments of executive functions; no improvement of word finding difficulties 3 months postoperative
40	R	CM (5)	tumour	Left gyrus temporo-occipitalis lateralis	Mild word-finding difficulties, no apparent comprehension problems, no signs of reading, writing, and calculation disorders, reduced verbal recall performance with normal verbal recognition performance
49	L	BW (6)	tumour	Right temporal lobe	No apparent word-finding difficulties, no comprehension problems, no signs of reading, writing, and calculation disorders; mild learning, recall, and recognition deficits for figural material; left hemisphere language lateralization in tachistoscopic visual half field examination

Table 1: Demographic characteristics of the stroke and tumour patients. Abbreviations: Pat.: Patient, Hand.: Handedness.

Experimental setup and stimuli

The study comprised two tasks (picture-word matching and lexical decision) that engage different linguistic processing abilities. Stimuli were presented in either an auditory and visual mode. The *picture/word matching task* consisted of line drawings of common objects together with a presentation of printed or spoken word that was either the name of the object or the name of a semantically related object. The control task consisted of pairs of random line drawings, taken from Kimura's Recurring Figures Test. There were 60 stimulus items in each of these three conditions. The *lexical decision task* consisted of written or spoken one- or two syllable words or pronounceable non-words. The control task comprised consonant strings with or without a "T". Each of the three conditions comprised 90 stimulus items.

Experimental Procedure and Task

Prior to scanning participants were informed about the experimental procedure. During scanning, subjects lay in a supine position and viewed the stimuli, which were back-projected onto a translucent screen, by way of a mirror mounted on the head coil. For the binaural stimulus presentation, we used an MR-compatible piezoelectric auditory stimulation system incorporated into standard Philips headphones.

In the picture-word matching task (Fig. 1), subjects had to decide whether the picture matched the word or whether the two line drawings are the same with a yes or no answer. In the lexical decision task (Fig. 2), participants had to decide whether the word was a word or a non word or whether the consonant strings contained a T with a yes or no answer. All stimuli were presented for 2 s. During the rest condition, subjects had to fixate a small cross displayed in the middle of the screen to prevent eye-movements.

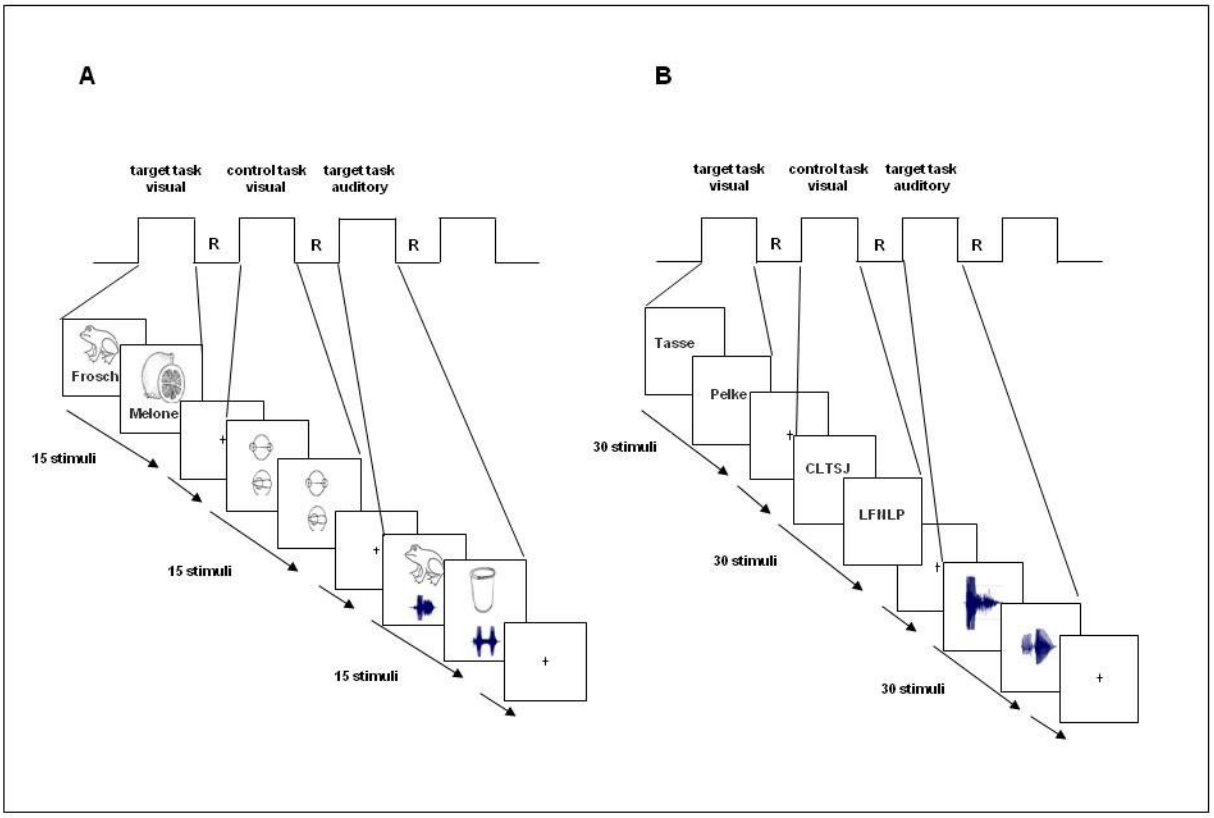

Fig. 1. Design of the word-picture matching (A) and the lexical decision task (B) with an example of each task/condition block.
A. In the visual target task, a printed word is presented below a picture, in the auditory target task a spoken word is presented with a picture. In both tasks a decision must be made as to whether the picture matches the presented word. In the visual control task the identity of the two figures must be judged.
B. In the visual target task, a printed word (Tasse) or pseudoword (Pelke) is presented, in the auditory target task words and pseudowords are presented via headphones during the presentation of a crosshair. In both tasks the lexical decision, the subject has to decide whether the presented word is a common German noun with a yes or no answer. In the visual control task, a decision must be made as to whether the consonant-string contains the letter T. Target and control tasks are separated by a 15s rest condition (R) in which a crosshair must be fixated.

For the two tasks we used a block design with the three task conditions (target task visual modality, target task auditory modality, control condition) presented pseudo-randomly. The picture-word matching task consisted of 30s periods of stimulus presentation alternating with 15s periods of rest (5 repetitions). The lexical decision task consisted of 60s periods of stimulus presentation alternating with 15s periods of rest (3 repetitions). Total scanning time was 540s for the picture-word matching task and 660s for the lexical decision task. During data acquisition accuracy of responses and reaction times were recorded simultaneously to assess the performance of the subjects. Presentation of the stimuli and recording of behavioural performance was done with *Presentation* (http://www.neurobs.com/). The left arm was positioned along the body.

Acquisition and analysis

MRI was performed in a 3.0 T MR system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an 8 channel SENSE™ head coil. For functional imaging a T2* weighted, single-shot, fast field echo, EPI sequence of the whole brain (TR = 3000ms, TE = 40ms, flip angle = 82°, FOV = 220mm × 220mm, acquisition matrix = 128 × 128, in plane resolution = 1.7mm × 1.7mm, slice thickness = 3mm, slice gap = 0, slices = 39) with a SENSE factor 2 was used (Pruessmann et al., 1999). Anatomical reference images of the whole brain were acquired at the end of the imaging session using a 3D, T1-weighted, field echo sequence (TR = 20ms, TE = 2.3ms, flip angle = 20°, in plane resolution = 0.9mm × 0.9mm, slice thickness = 0.75mm, 210 slices). These slices were transformed to iso-voxel size (1mm × 1mm × 1mm), and to Talairach space (Talairach and Tournoux, 1988).

Post-processing and data analysis was performed with the Brain Voyager QX 1.8 software package (Brain Innovation, Maastricht, The Netherlands). To remove unwanted signal components, data pre-processing was done for each subject prior to the computation of group analyses. Thereby, the standard parameters implemented in BrainVoyager QX 1.8 were adopted to diminish arbitrary selection of pre-processing parameters. Images were 3D motion corrected by means of trilinear interpolation. Spatial smoothing was performed by applying a Gaussian filter of 4mm FWHM, to allow for the integration of signals in an area of less than a centimeter. Within this range, smoothing merely reduces the noise by simultaneously enhancing the signal. Temporal smoothing included linear trend removal and high pass filter (limited to three cycles). Prior to group analysis, functional volumes were automatically co-registered to the individual three-dimensional structural scans and transformed into Talairach space (Talairach and Tournoux, 1988).

fMRI Analysis

For the single subject analysis the stimulation condition was modeled using a general linear model (GLM) convolved with the standard two gamma haemodynamic response functions resulting in t-contrast maps corrected for multiple comparisons with q(FDR) ≤ 0.01 showing the contrasts target versus rest (auditory modality), and target task versus control task (t=4, uncorrected). FDR (false discovery rate) is a recent development in statistical hypothesis testing to control the type I error (rejection of a true null hypothesis). FDR has a higher power than Bonferroni correction as the threshold varies automatically across subjects with consequent gain in sensitivity. The parameter q has the advantageous feature of being comparable across studies. The correction accounts for cluster size, i.e. the bigger the cluster the more unlikely are non-random activations hence a lesser correction is accounted for (Genovese, Lazar, & Nichols, 2002).

Results

Behavioural data

Table 2: Behavioural data of healthy subjects and patients in the word-picture matching task

	visual stimulus presentation	auditory stimulus presentation	control task	visual stimulus presentation	auditory stimulus presentation	control task
	same (n = 30)	dif (n = 30)	same (n = 29)	dif (n = 31)	same (n = 31)	dif (n = 29)
healthy controls (n = 16)	27.5*	24.7	27.5	26.5	29.6	27.9
Stroke patients						
Patient C.C.	29	26	28	29	30	29
Patient H.V.	25	13	25	8	29	27
Tumour patients						
R.L. preop	16	5	22	16	30	27
R.L. postop	24	17	29	18	30	27
C.M. preop	25	22	25	23	28	25
C.M. postop	28	22	25	25	30	25

* average number of correct decisions

Table 3: Behavioural data of healthy subjects and patients in the lexical decision task

	visual stimulus presentation	auditory stimulus presentation	control task	visual stimulus presentation	auditory stimulus presentation	control task
	same (n = 46)	dif (n = 44)	same (n = 46)	dif (n = 44)	same (n = 45)	dif (n = 45)
healthy controls (n = 16)	44.4*	40.7	40.9	37.1	43.5	44.7
Stroke patients						
Patient D.D.	13	35	14	28	42	44
Patient H.V.	43	34	34	34	36	45
Tumour patients						
C.M. preop	38	35	37	25	4	32
C.M. postop	45	43	39	37	42	43
B.W. preop	42	39	31	16	41	44
B.W. postop	43	41	38	36	45	45

* average number of correct decisions

fMRI data

Picture-word matching

Picture-word versus random line drawings (visual modality)

Controls

Figure 3 A illustrates an extended network of both peri- and extrasylvian areas that subserve picture-word matching when compared to random line drawings matching. Theses areas primarily reside on the left hemisphere, namely, the supplementary motor area, the premotor area, the inferior frontal sulcus, the inferior frontal gyrus (pars triangularis), the anterior insula, the superior temporal gyrus and the inferior occipital lobe. Bilateral activation was found in the middle temporal and the fusiform gyrus.

Picture-word versus rest (auditory modality)

Controls

The auditory matching task compared to rest revealed mainly bilateral activations in several peri-sylvian regions as the inferior frontal gyrus (pars opercularis), anterior insula, the Rolandic operculum and the superior temporal lobe (Fig. 3 B). Furthermore, stronger hemodynamic responses to the target task compared to rest were found in the bilateral middle temporal and fusiform gyrus, the inferior parietal and occipital lobe, in the left sensorimotor cortex, the right supplementary motor area and the right premotor cortex

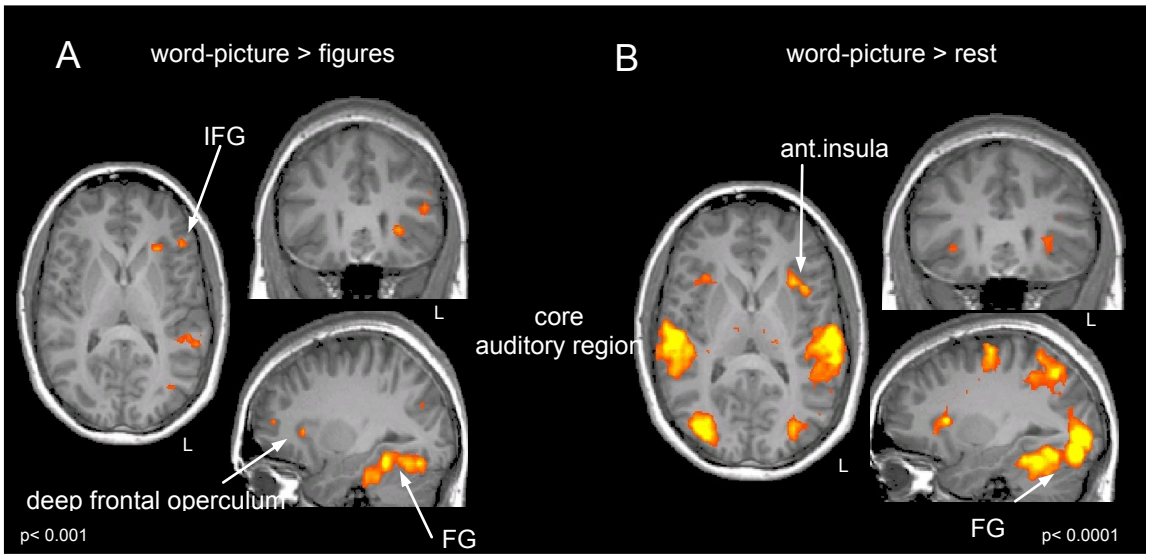

Fig. 3: Regions with significant activation for the contrasts visual word-picture-matching and random figure matching (t = 4, uncorrected) and auditory word-picture matching and rest (qFDR≤ 0.05 corrected), (healthy controls).

Lexical decision

Word versus consonant string (visual modality)

Controls

The contrast between words and consonant string (Fig 4) revealed significant BOLD-signal in the left hemisphere with three activation foci in the pars triangularis of the inferior frontal gyrus, and one in the pars triangularis. Further left hemispheric activation was found in the anterior insula, the middle temporal gyrus, the fusiform gyrus and the bilateral supplementary motor area.

Word versus rest (auditory modality)

As shown in Fig 4, bilateral activation was found in the anterior insula, the pars opercularis of the inferior frontal gyrus, the superior temporal and parietal lobe and the primary motor and premotor cortex. The activation of the supplementary motor area extended on both hemispheres. Stronger left lateralized hemodynamic response to heard word decision versus rest was found in the pars triangularis of the inferior frontal gyrus and the Rolandic operculum as well as in the primary sensory cortex.

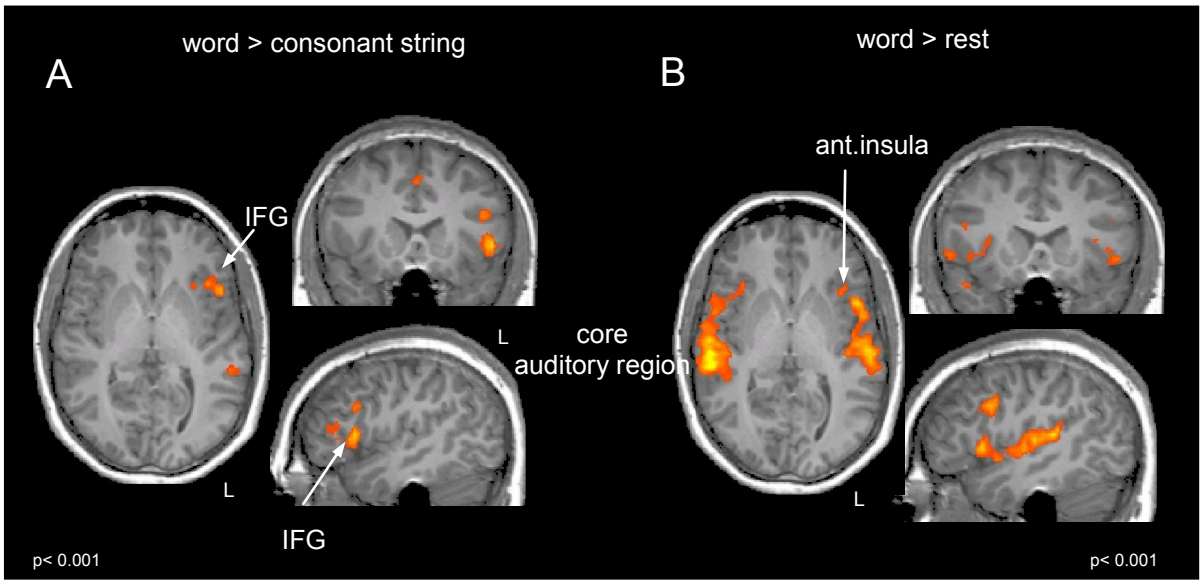

Fig. 4. Regions with significant activation for the contrasts visual lexical decision task and consonant letter detection (t = 4, uncorrected) and auditory lexical decision task and rest (qFDR≤ 0.05 corrected).

Table 4: Activation pattern of the stroke (1-3) and tumor (4-6) patients.

Patient	Contrast	Activation pattern	
Pat 1	**Picture-word matching**: Word versus figures (visual modality)	perilesional aSTL, bilateral IFG and PF, IT	
	Picture-word matching: Word versus rest (auditory modality)	bilateral and perilesional STL, MTL, ITL, right IFG, bilateral PM, bilateral IPL	
Pat 2	**Picture-word matching**: Word versus figures (visual modality)	perilesional aSTL, bilateral IFG and PF, predominantly left lateralized FG	
	Picture-word matching: Word versus rest (auditory modality)	bilateral and perilesional STL, ITL, left IFG, IPL	
	Lexical decision: Word versus consonant-string (visual modality)	perilesional aSTL, bilateral PF, predominantly left lateralized FG	
	Lexical decision: Word versus rest (auditory modality)	bilateral and perilesional STL, ITL, left IFG.	
Pat 3	**Lexical decision:** Word versus consonant-string (visual modality)	bilateral STL, PF	
	Lexical decision: Word versus rest (auditory modality)	bilateral IFG, STL, ITL	
Pat 4	**Lexical decision:** Word versus consonant-string (visual modality)	*Pre-surgical:* perilesional IFG, left ITL	*Post-surgical:* aIFG, pIFG
	Lexical decision: Word versus rest (auditory modality)	*Pre-surgical:* bilateral STL, ITL, IFG	*Post-surgical:* predominant right STL, left IFG, bilateral ITL
Pat 5	**Picture-word matching**: Word versus figures (visual modality)	*Pre-surgical:* bilateral IFG, left pSTL, ITL	*Post-surgical:* Bilateral IFG, left pSTL
	Picture-word matching: Word versus rest (auditory modality)	*Pre-surgical:* bilateral IFG, STL, ITL	*Post-surgical:* bilateral IFG, STL, ITL
	Lexical decision: Word versus consonant-string (visual modality)	*Pre-surgical:* bilateral IFG, aSTL	*Post-surgical:* bilateral IFG, STL
	Lexical decision: Word versus rest (auditory modality)	*Pre-surgical:* bilateral IFG, STL, FG, PM, IPL	*Post-surgical:* bilateral IFG, STL, FG, PM, IPL (reduced)
Pat 6	**Lexical decision:** Word versus consonant-string (visual modality)	*Pre-surgical:* bilateral IFG, STL, right PF	*Post-surgical:* bilateral IFG, STL, left FG, right PF
	Lexical decision: Word versus rest (auditory modality)	*Pre-surgical:* bilateral IFG, STL, FG, PF, PM	*Post-surgical:* bilateral IFG, STL, FG, PF, PM

FG: fusiform gyrus, ITL: inferior temporal lobe, IFG: inferior frontal gyrus, MTL: middle temporal lobe PF: prefrontal lobe, PM: premotor cortex, a/p STL: anterior/posterior superior temporal lobe.

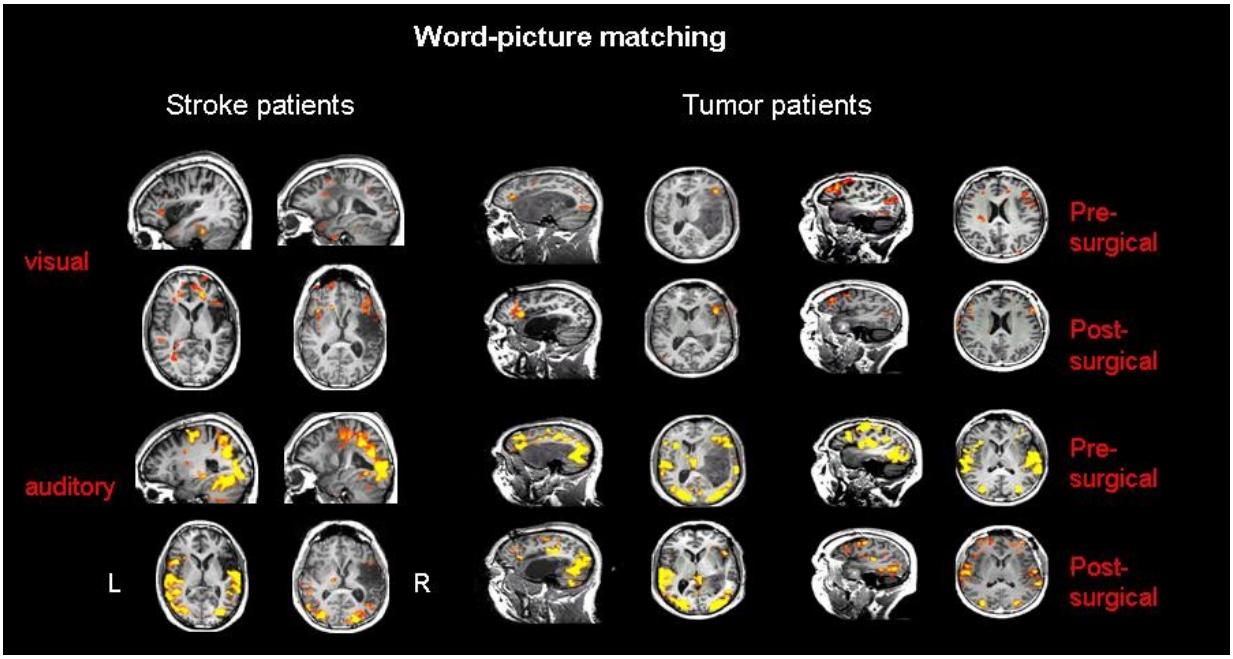

Fig. 5. Cortical activation pattern during picture word matching in two stroke (1, 2) and two tumor patients (4, 5).

Discussion

The present fMRI study aimed at investigating cerebral plasticity and the corresponding behavioural recovery in two groups of patients (stroke and tumour) with two language tasks previously assessed in healthy subjects (Keisker et al. in prep). The main questions were: How is the cortical activation pattern related to the observed behavioural performance and are plastic compensation processes different in patients with stroke compared to those with brain tumours. We suggested that the compensatory strategy of right-hemispheric integration is more often associated with improved language function in tumour patients, because the slowly growing tumour probably allows a shift of language functions to homologues sites on the right hemisphere.

Similarly to the group of healthy subjects (Keisker et al. in prep) there were overlapping and task-dependent brain responses in both patient groups. However, most of the patients showed (compensatory) activation in perilesional and contralateral areas (in addition to the brain responses observed in healthy controls). In the stroke patients, behavioural performance ranged from very successful and comparable to healthy subjects to very poor: e.g. an upregulation of undamaged tissue and / or recruitment of homologous language areas of the right hemisphere correlated with good behavioural performance in both tasks in patient 1. Whereas in patient 2 similar reorganization of the language network corresponded to behavioural performance dependent on the tasks demands (good performance in the lexical decision task and poor performance in the word-picture matching). In patient 3, selective impairment in language processing reflected a specific disruption of connectivity in the left hemisphere language network (poorer performance when the patient had to identify words, better performance when he had to identify non-words). In the tumour patients activation of the bilateral language network was correlated with comparable behavioural performance pre- and postoperatively in patient 5. In patient 4 the behavioural performance reflected the reduced right hemispheric processing abilities, particular evident with tasks where the patient had to identify non-matching pictures and words. Patient 6 showed reduced performance with auditory stimulus presentation.

In the following sections, the cortical activation pattern and behavioural performance of the two patient groups will be discussed in the context of the framework suggested by Price et al. (2006). It says that fMRI allows characterizing two types of abnormality in patients with neurological deficits: abnormal functional segregation and abnormal functional integration. Increased or decreased activation in one or a set of regions in patients relative to control subjects is defined as deficit in functional segregation. Abnormal functional integration, assessed with functional and effective connectivity among different regions, is implied with stronger or weaker influence of one brain region on another in patients relative to healthy

controls. The two types of abnormality are not strictly separated and investigations of abnormal functional integration help to explain abnormal functional integration.

Abnormal functional segregation

Although all of the investigated patients showed patterns of abnormal functional segregation, not all of them revealed abnormal behavioural performance. The different behavioural deficits were dependent on the task itself (picture-word matching versus lexical decision), parts of the task demands (e.g. matching versus non-matching picture and word), input modality, and lesion site. The various cases will be grouped and discussed according to their functional recovery.

Effective behavioural performance

Effective functional integration of (additionally activated) right hemispheric regions (mainly inferior frontal gyrus) was found in stroke and tumour patients: Whereas patient 1 showed behavioural performance in both tasks which was comparable to healthy subjects, patient 2 revealed functional integration of right hemispheric regions related to good performance in the lexical decision task. Similarly, one tumour patient had comparable behavioural performance pre-and postoperatively in both tasks. Based on the framework assumed by Hickok and Poeppel 2007 and the findings of the healthy subjects (Keisker et al. in prep.), lexical decision is suggested to preferentially activate cortical areas of the dorsal stream, including left parietal and frontal regions. The fact that patient 2 showed task-dependent effective functional integration of right hemispheric language related areas suggests that these regions successfully interact with the left hemispheric network involved in word retrieval. There are several studies reporting right hemispheric integration associated with improved language function either in stroke (Raboyeau et al. 2008; Winhuisen et al. 2005; 2007 Richter et al. 2008; Cao et al. 1999, Weiller et al. 1995) or in tumour patients (Thiel et al. 2006; 2005). Raboyeau et al. (2008) addressed the involvement of the right inferior frontal cortex in recovering aphasic patients and healthy subjects with learning foreign words as a challenging experimental situation in healthy subjects that may parallel word-finding impairments observed in aphasia as well as post training performance improvement. They postulated an involvement of the right inferior frontal cortex in both aphasic patients who benefited from intensive training of naming in their mother tongue and in healthy subjects trained to learn the same object names in foreign language. According to their results they suggested that enhanced activities in right-sided areas in aphasics is not the mere consequence of damage to left-sided homologues areas and could reflect the neural correlates of lexical learning also observed in control subjects.

Since patient 1 is a left hander with an extensive lesion in left temporal and frontal regions, the pre-morbid language lateralization remains an unresolved issue for the interpretation of his excellent performance in both tasks. However, the initially severe language deficits in this

patient suggest a possible pre-morbid left lateralized representation of language and consequently a very successful integration of right hemispheric language related areas. The good performance of patient 5 before and after surgical intervention in both tasks further strengthens the assumption that patients with slowly growing tumours may undergo functional reorganization as the outcome of tumour growth. In order to identify factors which determine the transfer of language function to the right hemisphere in patients with slowly growing left lateralized tumours, Thiel et al. (2006) assessed healthy and lesioned patients with PET and TMS during the performance of a verb generation task. Only patients with slowly progressing tumours recovered right-sided language function as detected by TMS. In patients with rapidly progressive lesions no right-sided language function was found and language performance was linearly correlated with the lateralization of language related brain activation to the left hemisphere. The authors concluded that time is the factor which determines successful integration of the right hemisphere into the language network for compensation of lost left hemisphere language function in that slowly progressive brain damage and long disease duration allows the shift of language function to homologues areas.

Poor behavioural performance

Poor performance with additional bilateral activation in language related areas was found in both stroke and tumour patients. Patient 2 (stroke) and patient 4 (tumour) had predominantly difficulties in the picture-word matching task when the picture and the word were different.

In the group of healthy subjects (Keisker et al. in prep), the pattern of activation associated with semantic retrieval during picture word matching was left lateralized and included posterior superior temporal cortex (BA 21/22), the anterior insula and pars triangularis (BA45). Since both patient 2 and 4 had an extensive lesion in the left temporal lobe, disconnection of the assumed ventral semantic stream connecting the posterior temporal regions and the inferior frontal cortex/ dorsolateral prefrontal cortex via the inferior occipito-frontal fasciculus (Duffau et al. 2005) requires support of right hemispheric structures. However, in case of non-matching word and picture, the right hemispheric integration of language related structures was less successful than with pictures and words that matched, suggesting that these language processes rely differently on left-hemispheric language structures. Similarly, Winhuisen et al. (2005) found poorer performance in a word picture matching tasks in post stroke aphasics who activated the homologous contralateral regions than in patients who recovered left hemispheric structures.

Abnormal functional integration and poor behavioural performance

Although no statistical analysis of functional and effective connectivity was performed in these patients, the site of the lesion, some patterns of cortical activation and the corresponding

behavioural recovery point to an abnormal functional integration of certain areas. Patient 3 who has a lesion at the left temporo-parietal junction causing symptoms of a conduction aphasia yielded very poor performance in the lexical decision task while judging a written or spoken real word. When the target stimulus was a pronounceable but meaning-less word, the performance was still below healthy subjects (especially in the auditory modality) but significantly better than with real words. This selective impairment reflects a specific disruption in the left hemisphere network especially of the dorsal stream (Hickok and Poeppel 2007), whose interaction is relevant for word-recognition (e.g. effect of familiarity) (Price 1996). Patient 6 is a special case insofar that she is a left-hander with a right temporal lobe tumour and left hemispheric language lateralization according to the tachistoscopic visual half field examination. The performance in the lexical decision task with auditory stimulus presentation was poor pre-surgically, improved slightly after surgical intervention but was still below the performance of healthy subjects. Speech *perception*, defined as the set of procedures that take acoustic input and derive representations that make contact with the mental lexicon—is assumed to be mediated in left and right auditory areas (Boemio et al. 2005; Poeppel et al. 2004). Thereby it is suggested that processes optimized for spectral analysis are more rightward lateralized, processes for temporal analysis more leftward (Poeppel et al. 2004, Poeppel 2003, Zatorre 2002) and the integration of slowly and rapidly changing acoustic cues during comprehension of spoken language is differentially mediated in the bilateral planum temporale (Meyer et al. 2004). Based on these findings, it can be suggested that the interplay between the right and left temporal (auditory) areas is affected in this patient. The fact that she performed well in the visual modality of the task further supports her assumed left lateralized language organization since lexical semantic processing beyond the perceptual level is supposed to be organized in a left lateralized anterior and posterior temporal network (Poeppel 2006).

Conclusion

The converging results show that reorganization following brain damage in stroke and tumour patients often includes perilesional and right hemispheric language related areas that support the spared network and help to overcome disconnected language systems. However, behavioural performance varied dependent on the task demand, input modality and lesion site. There was no apparent difference in the reorganization pattern between stroke and tumour patients in terms of reorganization patterns and the corresponding functional recovery. Effective integration of right hemispheric language related areas was observed in both groups, although there was a tendency for better behavioural performance in tumour patients.

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3.3 Study 3

Differential force scaling of fine-graded power grip force in the sensorimotor network

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Abstract

Force scaling in the sensorimotor network during generation and control of static or dynamic grip force has been the subject to many investigations in monkeys and human subjects. In human, the relationship between BOLD-signal in cortical and subcortical regions and force still remains controversial. With respect to grip force, the modulation of the BOLD-signal has been mostly studied for forces often reaching high levels while little attention has been given to the low range for which electrophysiological neuronal correlates have been demonstrated. We thus conducted a whole-brain fMRI study on the control of fine-graded force in the low range, using a power grip and three force conditions in a block design. Participants generated on a dynamometer visually-guided repetitive force pulses (ca 0.5 Hz), reaching target forces of 10%, 20%, and 30% of maximum voluntary contraction. Regions of interest analysis disclosed activation in the entire cortical and subcortical sensorimotor network and significant force-related modulation in several regions, including primary motor (M1) and somatosensory cortex, ventral premotor and inferior parietal areas, and cerebellum. The BOLD-signal however, increased monotonically with force only in contralateral M1 and ipsilateral anterior cerebellum. The remaining regions were activated with force in various nonlinear manners, suggesting that other factors, such as visual input, attention, and muscle recruitment also modulate the BOLD-signal in this visuomotor task. These findings demonstrate that various regions of the sensorimotor network participate differentially in the generation and control of fine-graded forces.

Introduction

The investigation of force scaling in primary motor cortex (M1) and other cortical and subcortical regions has started many decades ago with the pioneering contribution of Evarts (1968) who showed increased firing rate of M1 neurons during wrist flexion and extension opposing or assisting loads. This first study was followed by many others for wrist and elbow movements, precision grip and reaching movements (Cheney and Fetz, 1980; Conrad, et al. 1977; Evarts, et al. 1983; Georgopoulos, et al. 1992; Hepp-Reymond, et al. 1978, 1989; Riehle, et al. 1994; Smith, et al. 1975; Taira, et al. 1996; Thach, 1978). The reported relationships between neuronal firing and force as well as rate of force change were linear, sigmoid, or even logarithmic (see Ashe 1997 for review). During the control of fine-graded isometric force in precision grip, corticospinal and even corticomotoneuronal cells in M1 were monotonically increasing, but some were also decreasing their firing rate with force (Maier, et al. 1993). Moreover, similarly responding neurons were also found in the dorsal and ventral premotor areas (PMv, PMd), in primary somatosensory cortex (S1), in the cerebellum, thalamus and pallidum (Anner-Baratti, et al. 1986; Hepp-Reymond, et al. 1994, 1999; Smith

and Bourbonnais, 1981; Wannier, et al. 1991; Werner, et al. 1991), indicating that force is generated and controlled by a widespread cortical and subcortical network.

Several neuroimaging studies in humans investigated the brain areas responsible for the generation and control of force and, particular to fMRI methodology, the relationship between BOLD-signal changes and force (Boecker, et al. 2005; Cramer, et al. 2002; Dai, et al. 2001; Dettmers, et al. 1995, 1996; Ehrsson, et al. 2001; Kinoshita, et al. 2000; Kuhtz-Buschbeck et al. 2001, 2008; Ludman et al. 1996; Muley et al. 2001; Peck et al. 2001; Pope et al. 2005; Schmitz et al. 2005; Spraker et al. 2007; Thickbroom et al. 1998, 1999; Vaillancourt et al. 2003, 2004, 2007; Vaillancourt and Russell, 2002; van Duinen et al. 2008; Wexler et al. 1997). Some studies report monotonic activation increase while others failed to find a relationship between BOLD-signal and force. Several factors may account for these discrepancies. One potential reason relates to the question whether force was sustained for several seconds (static force) or whether repetitive force pulses (dynamic force) were exerted. Other important factors are the type of motor tasks or movements studied, e.g. whether or not they are guided by external cues (i.e., visual, auditory, tactile) and whether force is exerted in simple finger tapping, or isometrically in precision or in power grip, or for lifting weights. Finally, the selected force range is of utmost importance. High force recruits many muscles in the arm and thus the resulting brain responses may not be specific to the grip itself.

With respect to isometric power grip force the central control has been addressed in various studies (Begliomini, et al. 2007; Cramer, et al. 2002; Dai, et al. 2001; Ehrsson, et al. 2000; Floyer-Lea and Matthews, 2004, 2005; Kuhtz-Buschbeck et al. 2008; Liu, et al. 2004), and three of them have also looked systematically at the correlates between BOLD-signal and force. Dai et al. (2001), for static force ranging up to 80% MVC, reported monotonic increase in volume and signal intensity in several primary and secondary motor areas. Cramer et al. (2002) during repetitive squeezing at 1 Hz, showed some relationship between the number of pixels and percent signal change with peak force in the sensorimotor cortex and SMA, but with a large inter-individual variability. In both areas some subjects showed quite clear activation increase with force, which ranged up to 276 N, while others showed none, and BOLD increase mainly occurred at the high force level required. In the sensorimotor cortex, however, the correlation coefficient for the subject population reached the significance level due to the high number of activated pixels at high force (ca 90% MCV). Kuhtz-Buschbeck et al. (2008), comparing power and precision grip, tested the relation between the BOLD-signal and force pulses within the low force range and found linearity in M1 and the cerebellum. However, their measurements included only two force levels.

So far the data on force control in power grip suggest that the BOLD-signal does not reflect as well dynamic force pulses as static force. They also imply that high force pulses recruit many

hand and arm muscles, thus contributing to the larger volumes and signal intensity of BOLD activation. As neuronal correlates for low and fine-graded forces have been revealed in conscious monkeys (Ashe, 1997; Evarts, et al. 1983; Hepp-Reymond, et al. 1989), we wondered whether a better modulation of the BOLD-signal could occur for force pulses within a low range. In the clinic, simple and precise tools are used to quantify the recovery of function over time after a stroke, one important function being force in hand and fingers, and to understand the processes occurring during rehabilitation. We have thus decided to test force scaling in cortical and subcortical motor regions for force pulses in power grip within a low force range, using fMRI and a visuomotor paradigm. To measure force accurately, a special MR-compatible device with optical measurement providing a high degree of reproducibility, even in the low force range, was used. The main objective was to find out whether the BOLD-signal correlates with force, whether the force scaling is linear, and whether it behaves the same way in all the areas involved in generation and control of force.

Materials and Methods

Participants

Fourteen healthy subjects (seven females, seven males, age range: 21-33 years) without any history of neurological or psychiatric disorder were recruited for this study. Hand dominance according to the Edinburgh-handedness inventory (Oldfield, 1971) showed right-hand dominance. All participants gave their written consent, and the study was approved by the local ethics committee.

Force measurement device

The power grip was measured with a custom made MR-compatible dynamometer developed by the Sensory-Motor Systems Laboratory of ETH Zurich (http://www.mrsensor.ethz.ch / Fig. 1). It is based on the optical force measurement principle and consists of a plastic handgrip containing optical fibres that transmit laser signals to an interface box, which produces analogue and digital force outputs. The measured signal is a quasi-linear function of the applied force. Multi-point calibration in the processing unit ensures good linearity and accuracy of the force sensor. The dynamometer was individually calibrated for each subject. It is easy to install into any experimental fMRI environment, easy to use, and can be synchronized with other recording processes.

Activation paradigm

Subjects were holding with the right hand the dynamometer shown in Fig. 1 with the thumb opposing the four other fingers, i.e. in power grip. They were asked to generate isometrically

repetitive visually-guided force pulses at a rate of ca 0.5 Hz, reaching target forces of 10%, 20% and 30% of their maximum voluntary contraction (MVC). Visual feedback was displayed on a screen in front of the subject. On a blue background, target and exerted forces were visualized as two grey concentric rectangles in which the colour of the inner square (exerted force) had to match the colour of the outer square (target force). The stronger the force was the darker was the grey. The task was practiced prior to the scanning procedure to ensure accurate execution. A block design with 21 s periods of rest alternating with 21 s for each force condition was used. The three force conditions were presented in a pseudo-random order (ABCCBAACBBACABC, with A = 10%, B = 20%, C = 30% MVC) and repeated 5 times. During the control condition, subjects had to fixate a small cross displayed in the middle of the blue screen to prevent eye-movements. Prior to training, the MVC was assessed for each subject and the MR-compatible handgrip was then accordingly calibrated. During scanning, the subjects hold their right arm in a comfortable slightly flexed position, at an angle of approximately 90° relative to their upper arm with the left arm positioned along the body. The output of the MR-compatible handgrip was recorded simultaneously with the fMRI data acquisition.

fMRI-Acquisition and post-processing

MRI was performed in a 3.0 T MR system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an 8 channel SENSE™ head coil. For functional imaging a T2* weighted, single-shot, fast field echo, EPI sequence of the whole brain (TR = 3000ms, TE = 40ms, flip angle = 82°, FOV = 220mm × 220mm, acquisition matrix = 128 × 128, in plane resolution = 1.7mm × 1.7mm, slice thickness = 3mm, slice gap = 0, slices = 39) with a SENSE factor 2 was used (Pruessmann et al., 1999). Anatomical reference images of the whole brain were acquired at the end of the imaging session using a 3D, T1-weighted, field echo sequence (TR = 20ms, TE = 2.3ms, flip angle = 20°, in plane resolution = 0.9mm × 0.9mm, slice thickness = 0.75mm, 210 slices). These slices were transformed to iso-voxel size (1mm × 1mm × 1mm), and to Talairach space (Talairach and Tournoux, 1988).

Post-processing and data analysis was performed with the Brain Voyager QX 1.8 software package (Brain Innovation, Maastricht, The Netherlands). To remove unwanted signal components, data pre-processing was done for each subject prior to the computation of group analyses. Thereby, the standard parameters implemented in Brain Voyager QX 1.8 were adopted to diminish arbitrary selection of pre-processing parameters. Images were 3D motion corrected by means of trilinear interpolation. Spatial smoothing was performed by applying a Gaussian filter of 4mm FWHM, to allow for the integration of signals in an area of less than a centimeter. Within this range, smoothing merely reduces the noise by simultaneously enhancing the signal. Temporal smoothing included linear trend removal and high pass filter

(limited to three cycles). Prior to group analysis, functional volumes were automatically co-registered to the individual three-dimensional structural scans and transformed into Talairach space (Talairach and Tournoux, 1988).

Data-Analysis

For the single subject analysis the stimulation condition was modeled using a general linear model (GLM) convolved with the standard two gamma haemodynamic response functions resulting in t-contrast maps corrected for multiple comparisons with q(FDR) ≤ 0.01 showing the contrast force (e.g. 10%, 20%, 30% MVC) vs. a resting condition. FDR (false discovery rate) is a recent development in statistical hypothesis testing to control the type I error (rejection of a true null hypothesis). FDR has a higher power than Bonferroni correction as the threshold varies automatically across subjects with consequent gain in sensitivity. The parameter q has the advantageous feature of being comparable across studies. The correction accounts for cluster size, i.e. the bigger the cluster the more unlikely are non-random activations hence a lesser correction is accounted for (see Genovese, et al. 2002).

For the group analysis, the significance level was set at qFDR ≤ 0.01. A two-step analysis was performed on the basis of the linear model. A random effect analysis was performed using the multi-study option of the analysis software to detect the brain regions involved in the visuomotor task. For each force level (10%, 20%, 30% MVC) group activations were compared to rest. The whole brain analysis identified regions responding more strongly to the generation of the three forces than to baseline. The statistical threshold for the whole brain analysis was t = 4.5 (qFDR ≤ 0.01 corrected).

Following the group analysis, we also performed a post-hoc region of interest (ROI) analysis, which enables to test whether BOLD responses obtained from distinct regions of the visuomotor network may vary as a function of force. ROIs were defined based on the whole brain activation patterns obtained from the contrast between all three forces summed together (10% +20% +30% MVC) and rest, with a statistical threshold of t = 4.5 (qFDR ≤ 0.01 corrected). Peaks of activation in each region were identified and significant voxels surrounding those peaks were selected and defined as ROIs (5mm × 5mm × 5mm). For each ROI, group statistical analysis was performed by using the GLM option in the analysis software and for each force level and each participant beta values were obtained. These beta values were then subjected to ANOVAs with factors region and force (see Results section).

Behavioural data analysis

To assess the motor performance, four parameters were computed: peak force per block and force level (measured for each force pulse from the baseline to the maximal force), integrated sum of exerted force (surface under the force traces), number of force pulses per block, and

the first derivative of the force (dF/dt measured for each force pulse). The obtained measures were compared and checked for variance.

Results

Behavioural results

The analysis revealed that for the three parameters, peak force, integrated force, and number of pulses per block, the values of the five blocks were comparable despite the pseudo-random presentation order. The most reproducible force parameter chosen for comparison with the functional data was the mean peak force. The correlation between the first derivative of force dF/dt and the mean peak force assessed by the Pearson's correlation coefficient was also highly significant ($r = 0.851$, $P \leq 0.01$). To assess the intra-individual variance of subjects' force production, the peak force of each pulse per block and force level was measured. These data were subjected to a one-way ANOVA which showed that the intra-individual variance reached significance more frequently in the lower force range (10% and 20% MVC) than in the 30% MVC range.

To check for significant differences between the three force levels, the mean peak forces per block and force level for all the subjects (15 values for 13 individuals and 14 for one) were subjected to another one-way ANOVA. The differences between the conditions were highly significant ($F_{2,206}$) = 363.73, $P \leq 0.000$). These findings indicate that the three mean peak forces did not overlap and that the inter- and intra-individual variability had no significant influence.

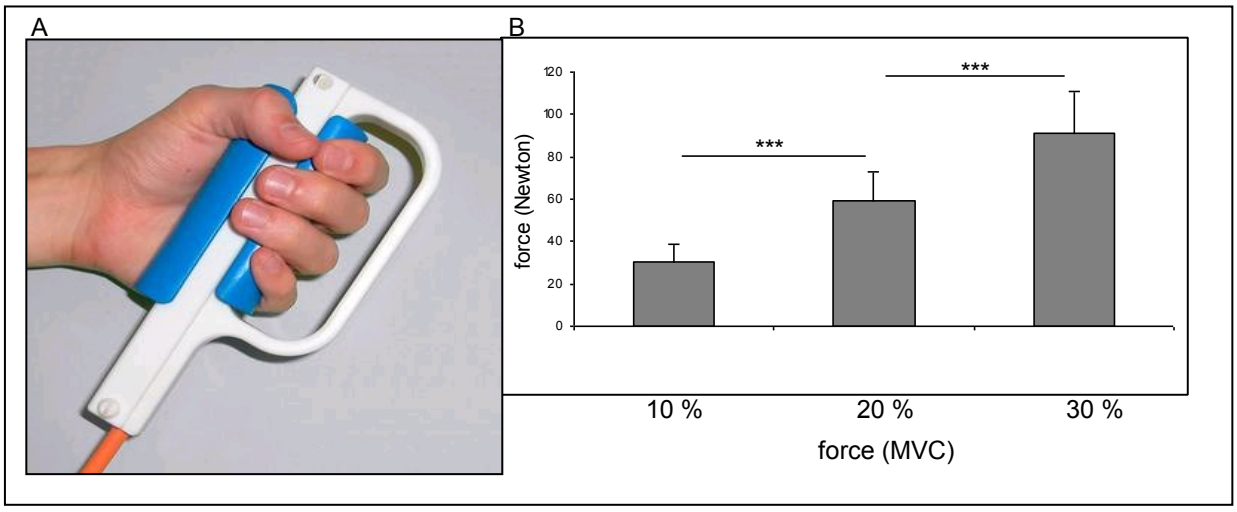

Fig 1. A. MR-compatible dynamometer. B. Mean peak forces and standard deviations for the three force levels (14 subjects).

We also investigated whether the frequency of the force pulses may influence the haemodynamic response, by assessing the number of pulses per block and force condition in each subject. In most subjects the variability of the number of pulses per force level was minimal. However, changes in the frequency of the force pulses were registered between different force levels. In most subjects (11 out of 14), a negative relationship between the mean number of pulses and mean peak force was observed. Two subjects had equal mean frequency values for 20% and 30% MVC, and the last subject had the highest pulse number at the highest force level.

The integrated sum of exerted force behaved in a very similar way as the peak force but was more variable, and for this reason was discarded from further analysis.

fMRI results

Whole brain analysis

The three forces (10%, 20%, 30% MVC) elicited overlapping BOLD activations in a widespread sensorimotor network, including bilateral frontal and parietal cortical areas and subcortically, the cerebellum and basal ganglia (statistical threshold $t = 4.5$, qFDR ≤ 0.01 corrected). Significant frontal activations were found contralaterally in M1, bilaterally in the supplementary and cingulate motor areas (SMA and CMA resp), and in (PMv), and ipsilaterally in the anterior insula. Parietal activations revealed three significant foci, namely one in the contralateral (S1) and two in the ipsilateral inferior parietal lobule (IPL). Subcortical activations included the ipsilateral pallidum (GP) and the cerebellum, ipsilaterally in its anterior-medial part (Larsell's lobule III, IV, Larsell and Jansen, 1972) and bilaterally in the posterior hemisphere (lobule VI, VII). The coordinates of the centres of gravity, the average t-values and the volumes of the activated regions are listed in Table 2 and the areas are illustrated in Figure 2.

	Left hemisphere					Right hemisphere				
Anatomical region	T-value	x	y	z	volume	T-value	x	y	z	volume
M1	7.04	-36	-25	54	6545					
S1	5.97	-46	-30	48	6424					
SMA						5.82	1	-6	57	1792
CMA						5.02	6	7	50	362
PMv	5.02	-51	3	32	405	6.09	50	4	37	1945
PMv	5.35	-43	2	11	679	5.53	53	8	13	2434
pallidum						5.24	21	3	10	337
ant Insula						5.12	35	17	10	300
IPL						6.15	49	-36	44	2945
IPL						6.13	35	-45	42	1862
ant CB						6.53	17	-50	-18	3703
post CB	6.02	-31	-59	-21	3259	11.9	28	-58	-18	2762

Table I. Mean t-values, coordinates of the centres of gravity (Talairach and Tournoux, 1988), and volumes of activated tissue of the regions with significant activation (t = 4.5, FDR 0.01 corrected) for the contrasts 10% +20% +30% MVC versus baseline in 14 subjects.

M1: primary motor cortex; S1: primary somatosensory cortex; SMA: supplementary motor area; CMA: cingulate motor area; PMv: ventral premotor cortex; IPL: inferior parietal lobe; CB: cerebellum.

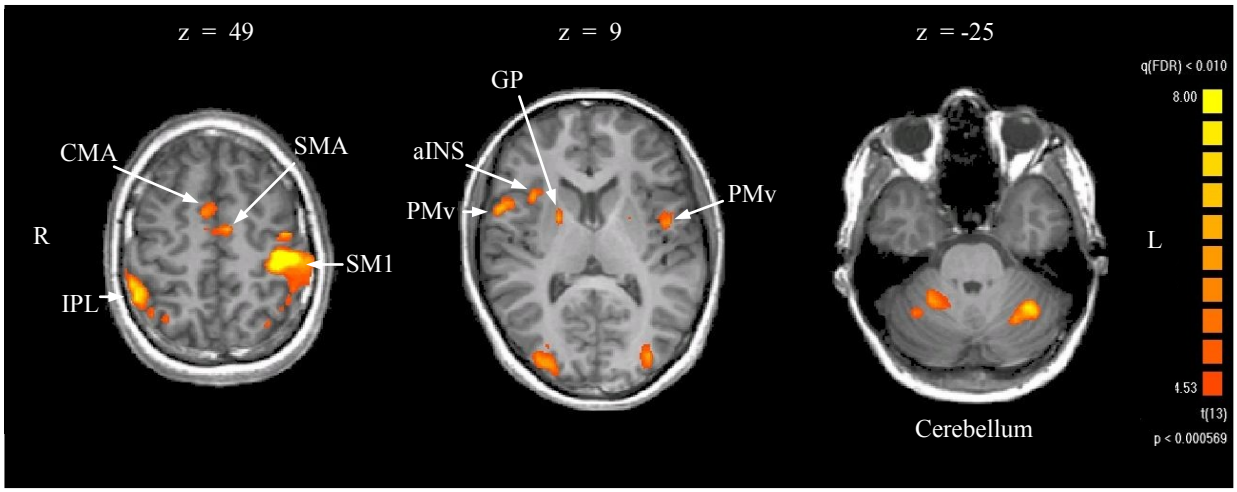

Fig. 2. Transversal sections showing activation patterns obtained for the three forces versus baseline. M1: primary motor cortex, S1: primary somatosensory cortex, SMA: supplementary motor area, CMA: cingulate motor area, aINS: anterior insula, PMv: ventral premotor cortex, IPL: inferior parietal lobe, GP: pallidum

ROI analysis (group analysis)

Fifteen ROIs were functionally identified in the two hemispheres (see Methods). The beta values obtained from the ROI analysis were subjected to a two-way ANOVA with factors *force* × *ROI* (3 × 15) that revealed a main effect of *force* ($F_{1,2}$) = 8.64, P ≤ 0.005, a main effect of *ROI* ($F_{1,14}$) = 10.18, P ≤ 0.000, and interaction of *ROI* and *force* ($F_{2,28}$) = 4.4, P ≤ 0.000. Based on these data we performed a separate one-way ANOVA for each of the 15 ROIs. A main effect of force was found in 9 ROIs, namely contralateral M1 and S1, bilateral PMv, right IPL (2 foci), right anterior and bilateral posterior cerebellum. Talairach and Tournoux (1988) coordinates of the activation peaks, maximum t-values, means and standard errors (in parentheses) of the beta values for these 9 ROIs are listed in Table 2.

Anatomical region	Side	x	y	z	t-value	10 % MVC	20% MVC	30% MVC
M1	L	-36	-25	55	20.2	6.0 (0.7)	6.8 (0.6)	8.9 (0.8)
S1	L	-45	-22	49	12	4.1 (0.5)	4.2 (0.5)	5.7 (0.6)
PMv	L	-42	-4	13	9.2	3.7 (0.5)	2.7 (0.4)	3.6 (0.6)
PMv	R	57	8	8	8.4	4.9 (0.9)	3.2 (0.7)	5.5 (1.4)
IPL	R	45	-40	46	10.4	3.5 (0.4)	2.9 (0.5)	4.2 (0.4)
IPL	R	36	-40	40	12.2	3.0 (0.4)	2.4 (0.3)	3.6 (0.4)
ant CB	R	11	-52	-17	12.9	3.4 (0.5)	4.3 (0.6)	6.1 (0.6)
post CB	L	-36	-52	-23	9.6	4.3 (0.8)	4.2 (0.7)	5.4 (0.9)
post CB	R	30	-67	-17	13.4	5.5 (0.7)	5.6 (0.7)	6.6 (0.6)

Table 2. Significant (t = 4.5, FDR 0.01 corrected) activation foci for the three forces versus rest obtained in the ROI analysis: Talairach and Tournoux (1988) coordinates of the activation peaks, the maximum t-values, the mean and standard error (in parentheses) of the beta weights for each ROI and force are depicted.Abbr.: see Table 1

To determine the relationship between the BOLD-signal and force within these distinct regions, the beta values obtained for the three forces were then tested against each other with paired sample t-test (Table 3).

Anatomical region	Side	20% vs. 10%	30% vs. 20%	30% vs. 10%
M1	L	P ≤ 0.04	P ≤ 0.001	P ≤ 0.0001
S1	L	ns.	P ≤ 0.001	P ≤ 0.0001
PMv	L	P ≤ 0.05	P ≤ 0.06	ns.
PMv	R	P ≤ 0.05	ns.	ns.
IPL	R	ns.	P ≤ 0.001	ns.
IPL	R	ns.	P ≤ 0.005	P ≤ 0.04
ant CB	R	P ≤ 0.06	P ≤ 0.001	P ≤ 0.0001
post CB	L	ns.	P ≤ 0.06	P ≤ 0.005
post CB	R	ns.	P ≤ 0.05	P ≤ 0.004

Table 3. Comparison between force levels. Significant difference of beta weights for each ROI in the paired sample t-test.

Abbr.: see Table 1

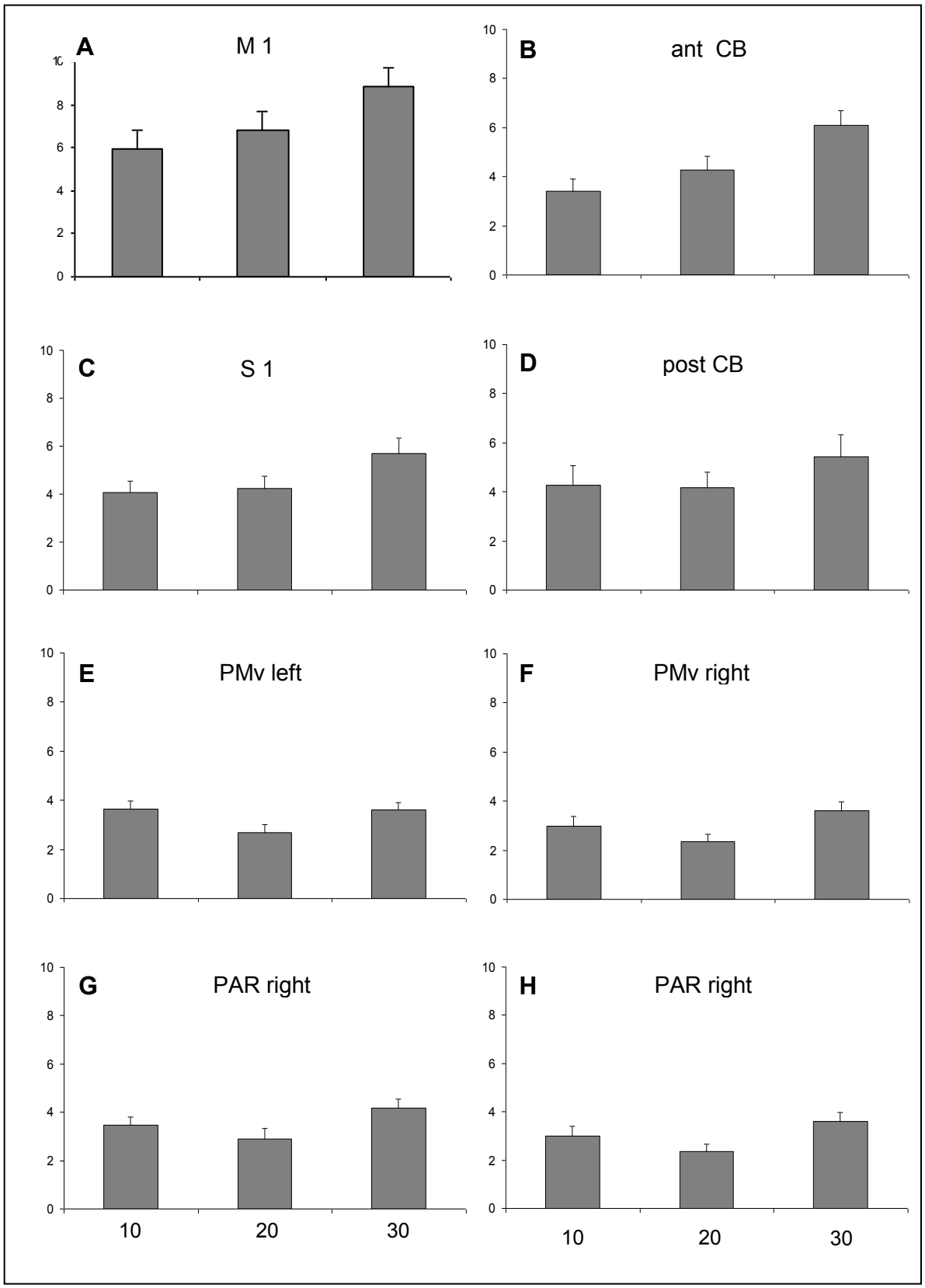

Fig 3. Mean and standard error of the beta weights (y-axis) collected for each force level (x-axis) in left primary motor cortex (A), right anterior cerebellum (B), left somatosensory cortex (C), left posterior cerebellum (D), left and right ventral premotor cortex (E,F) and right inferior parietal cortex (G, H).

Linear and non linear correlation between BOLD-signal and force

Figure 3 displays for eight ROIs the mean beta values obtained for each force level (10%, 20%, and 30% MVC) averaged over the 14 subjects. As one can see (Fig. 3A), task-related activation in M1 increased linearly as a function of increasing grip strength. The beta values obtained for the three forces reached the highest values compared to the other ROIs and increased from the lowest to the highest force in a monotonic fashion. In the anterior cerebellum (Fig. 3B), the BOLD-signal increased with force in a similar manner as in M1, although the differences in beta values between 10% and 20% MVC were only close to significance. In contrast, the beta values in S1 (Fig. 3C) and posterior cerebellum (Fig. 3D) did not increase monotonically. Since the beta values of both foci in posterior cerebellum behaved similarly, only one of them is displayed in the Figure 3. In these three regions, almost the same beta values were obtained for 10% and 20% and an increase occurred only for 30% MVC. Finally, in left and right PMv (Fig. 3E, F), as well as in the two foci of the right IPL (Fig. 3G, H), similar relationships between peak force and beta values were noticed, namely a high cortical activation during 10%, a significant decrease for 20%, followed by a strong increase for 30% MVC (Table III). Bilateral PMv regions and the two IPL foci had the lowest beta values.

For the eight ROIs shown in Fig. 3, linear correlation between the beta values and mean peak force and the first derivate of force dF/dt were assessed by the Pearson's correlation coefficient and considered significant for $P \leq 0.05$. As illustrated in Figure 4, the beta values in most ROIs were positively correlated for both, peak force and dF/dt, but the significance level was reached only in M1, S1, and anterior CB, i.e. for the peak force (M1, $r = 0.44$, $P \leq 0.01$; S1, $r = 0.31$, $P \leq 0.05$; anterior CB, $r = 0.4$, $P \leq 0.05$) and for dF/dt (M1 ($r = 0.32$, $P \leq 0.01$; S1, $r = 0.34$, $P \leq 0.05$; in anterior CB, $r = 0.45$, $P \leq 0.05$). To test whether the number of force pulses had an influence on the resulting BOLD-signal, we also correlated the beta values with the number of force pulses. In four of eight ROIs, namely M1, left PMv, and the two IPL foci, the beta-values negatively correlated with the number of force pulses, in three of them even significantly (M1, $r = -0.35$, $P \leq 0.01$, PMv left $r = -0.32$, $P \leq 0.05$, IPL right $r = -0.55$, $P \leq 0.01$).

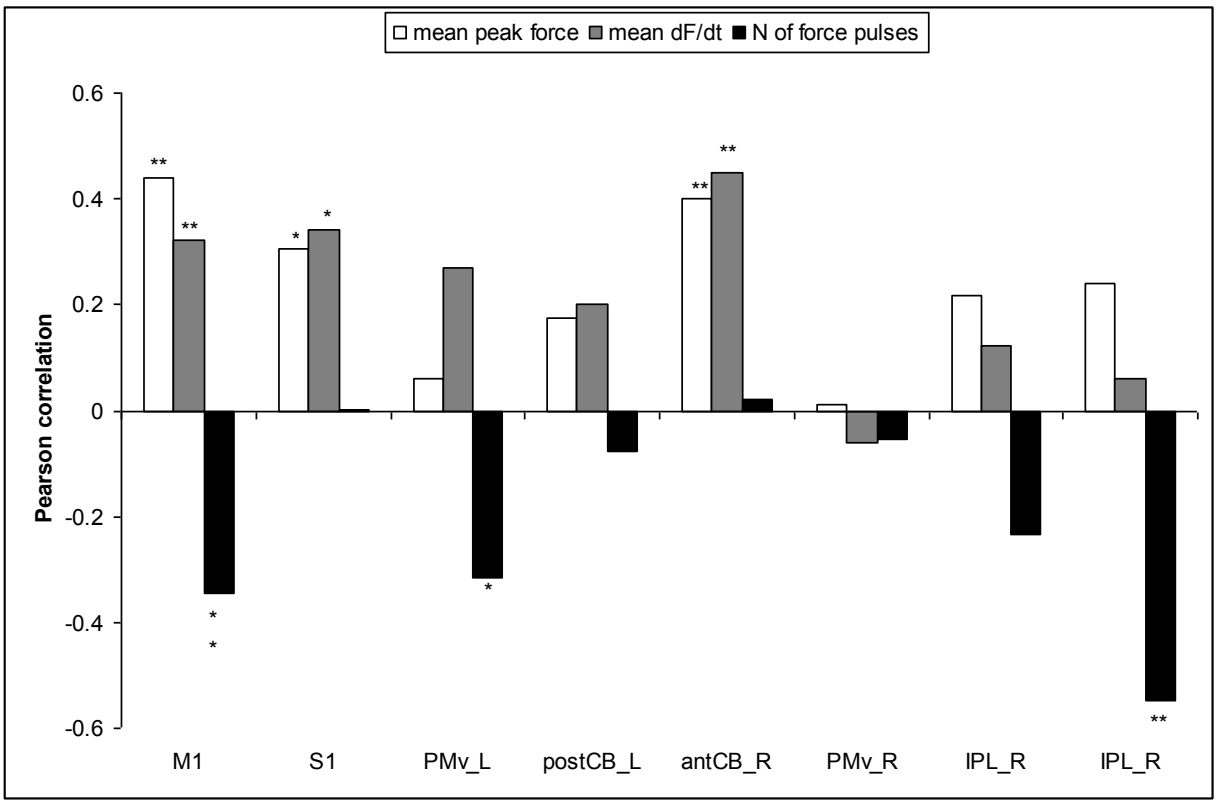

Fig. 4. Pearson correlation coefficients between the beta values of 8 ROIS and mean peak forces (white columns), mean dF/dt (grey columns) and mean number of force pulses (black columns) for the 14 subjects. ** P ≤ 0.01, * P ≤ 0.05. Abbr.: see legend Fig. 2.

Single subject ROI analysis in M1

Single subject ROI analysis was performed to better understand the nature of the linear force scaling in M1 and the potential influence of the number of force pulses. In most subjects (10/14) the increase of the beta values with applied force was linear, with correlation coefficients between 0.88 and 1.0. Nine out of these 10 subjects, showed strongly negative relationships between beta values and number of force pulses (correlations coefficients between 0.87 and 0.99). The four remaining subjects shown in Figure 5 did not display any monotonic increase between beta values and the three peak forces, but in two out of these four a strong activation increase occurred for 30% MVC (VP2 and VP3). In these four subjects the relationship between beta values and number of force pulses showed the same negative tendency as in the other 10 (VP1 r = -0.13 , VP2 r = -0.37, VP3 r = -0.68, VP4 r = -0.12).

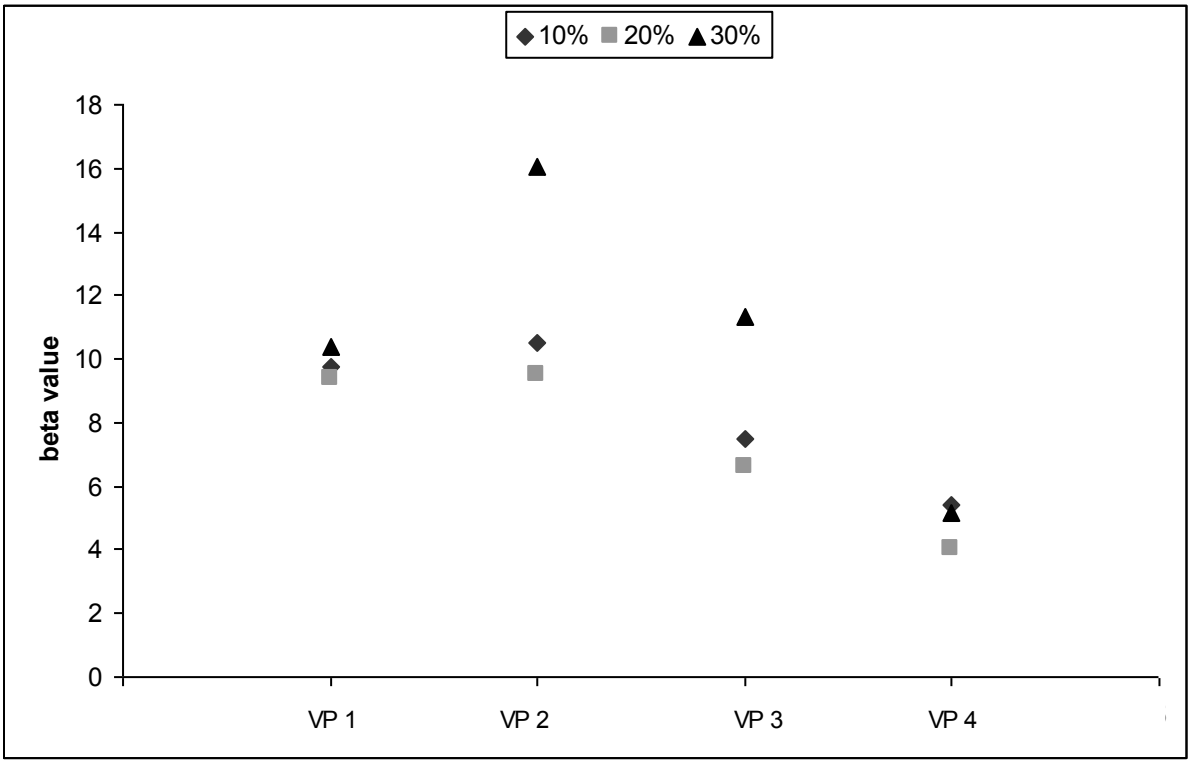

Figure 5. Beta values in primary motor cortex (M1) for the four subjects (VP1, 2, 3, and 4) who showed no linear relationship between beta values and force.

Discussion

The aim of the present study was to understand how the scaling of a low range, visually-guided force is reflected in various regions of the sensorimotor network of healthy humans. We report three major observations for dynamic force in power grip. First, we confirm that power grip activates all motor cortical and subcortical regions. Second, brain activation is modulated by the force amplitude in several, but not all regions, including contralateral M1 and S1, bilateral PMv and inferior parietal areas IPL, and cerebellum. The third and most important finding shows that within these regions only two showed a linear scaling of the BOLD-signal with grip-force, namely M1 and anterior cerebellum. In all other force-related areas, i.e. PMv, S1, IPL, and posterior cerebellum, the scaling is non-linear, showing either an activation increase only at the highest force level or even more complex modulations. Brain activation did not correlate positively with the rate of force in any of the regions where brain activation was modulated by force. These findings lead to the following conclusions; force is differentially represented in various sensorimotor regions; cortical activation does not necessarily increase as a function of power grip strength; other factors, such as visual input, instruction, and attention may modulate brain activation in visuomotor tasks.

Cortical and subcortical regions activated by power grip

A large number of cortical and subcortical areas were activated by the visuomotor task. Most regions have already been described in previous brain imaging studies on force control, mainly related to precision grip (Ehrsson, et al. 2000, 2001; Pope, et al. 2005; Spraker, et al. 2007; Vaillancourt, et al. 2003, 2004, 2006, 2007) and more rarely to power grip (Cramer, et al. 2002; Dai, et al. 2001; Ehrsson, et al. 2000; Kutz-Buschbeck et al. 2008) and index finger or wrist movement (Dettmers, et al. 1995, 1996; Ludman, et al. 1996; Peck, et al. 2001; Thickbroom, et al. 1999). Thus, our data confirm task-related activation in contralateral M1 and S1, in SMA/CMA, in parietal and premotor regions, mostly bilaterally, as well as in basal ganglia and cerebellum. In these previous investigations force-related activation was mainly reported for the control of static force, i.e. for forces, which had to be maintained for several seconds (Dai, et al. 2001; Kuhtz-Buschbeck, et al. 2001; Peck, et al. 2001; Spraker, et al. 2007; Thickbroom, et al. 1999; Vaillancourt, et al. 2003, 2004, 2006). Only a few studies addressed dynamic force generated either with finger flexion or wrist movements (Dettmers, et al. 1995, 1996; Ludman, et al. 1996; Peck, et al. 2001; Ramnani, et al. 2001; Thickbroom, et al. 1999; van Duinen et al. 2008) or with precision and power grip (Cramer, et al. 2002; Ehrsson, et al. 2000; Pope, et al. 2005; Vaillancourt, et al. 2004, 2006).

From all the regions showing task-related activation in our study, force increase was associated with significant BOLD-signal changes only in nine sites, i.e. contralateral M1 and S1, right IPL (2 foci), bilateral PMv and cerebellum (3 foci). In contrast, the strong activation in medial motor structures (SMA/CMA), did not correlate with the amplitude of the dynamic force pulses. It is interesting to mention that, in early neurophysiological investigations in monkeys exerting force in precision grip, single cell firing rate in SMA/CMA was poorly related to force (Cadoret and Smith, 1997; Smith, 1979). The lack of modulation within the low force range in SMA is in accordance with the findings of Cramer et al. (2002) showing force-related increase in BOLD-signal only in some subjects, mainly between medium and hard squeeze. However, these data are at odd with Dai et al. (2001) who reported that for a static handgrip the amplitude of the BOLD-signal was directly proportional to the degree of muscle activation in several motor cortical fields including SMA and with those of van Duinen et al. (2008) for isometric contraction of the first dorsal interosseus muscle. Major differences in the control of static and dynamic force pulses and in the force range tested may account for this discrepancy. Similarly, we found no positive regression coefficients between the activation in the basal ganglia and the exerted force, which contrasts with a recent investigation by Spraker et al. (2007) showing positive increase in BOLD-signal with static force in pallidum and subthalamus over a broad force range.

Linearity between power grip force and BOLD-signal

Primary Motor Cortex

In the group analysis, the BOLD-signal in contralateral M1 increased linearly as a function of grip strength. This finding is supported by several human brain mapping studies (Cramer, et al. 2002; Dai, et al. 2001; Dettmers, et al. 1995, 1996; Ehrsson, et al. 2001; Peck, et al. 2001; Vaillancourt, et al. 2004) reporting significant correlations between force or electromyogram (EMG) and number of activated pixels and/or average signal intensity. Interestingly, in almost all subjects tested by Cramer et al. (2002) a clear activation increase mainly occurred between the medium and hard squeeze levels, which is in concordance with our observations. Three main factors may account for the stronger BOLD-signal with higher force. First, increased firing rate of corticospinal neurons as being repeatedly reported in conscious monkeys (Ashe, 1997; Cheney and Fetz, 1980; Evarts 1968; Hepp-Reymond, et al. 1978; Maier, et al. 1993; Smith, et al. 1975). Second, recruitment of a larger number of M1 neurons with higher forces, resulting in an increase in activation volume. Lastly, increased somatosensory feedback due to stronger stimulation of cutaneous receptors in the glabrous skin of the hand (Johnson-Frey, 2004; Witney, et al. 2004) and of proprioceptors associated with higher grip force. This stimulation may lead to increased input to the M1 neurons, either directly via the thalamus, or indirectly via S1 and corticocortical connections, and is supported by our finding that power grip force at 30% MVC produced the strongest fMRI signal in S1.

In some previous human imaging studies the relation between BOLD-signal increase in M1 and dynamic force did not reach significance and often only the volume of activation but not the intensity of the signal showed an increment (Ehrsson, et al. 2001; Ludman, et al. 1996; Thickbroom, et al. 1999). This discrepancy can be attributed to differences in the range of force applied and the movements tested. In Thickbroom et al. (1999) the motor task consisted of generating force in finger flexion within a relatively low and narrow force range. Nevertheless, the lack of significant activation increase in M1 with a force increase from 5% to 10% MVC in this investigation, is comparable to our data showing less significant BOLD-signal increase between 10% and 20% MVC than between 20% and 30% MVC. However, these findings are at odd with single cell studies which, for a precision grip task, revealed linear regression coefficients for static and fine-graded low force (Ashe, 1997; Hepp-Reymond, et al. 1978, 1999; Maier and Hepp-Reymond, 1995; Wannier, et al. 1991). The differences between neuroimaging and electrophysiological studies suggest that the BOLD-signal in M1 does not always simply reflect dynamic force within a low range. It may also be modulated by other factors, such as attention required for the precise force control, leading to activation increase in sensorimotor cortical areas, including M1 (Binkofski, et al. 2002; Ehrsson, et al. 2001; Indovina and Sanes, 2001; Johansen-Berg and Matthews, 2002; Rowe, et al. 2002).

Anterior cerebellum

The importance of the cerebellum in controlling grasping is well known in clinical neurology (Holmes, 1917) but cerebellar neural correlates related to grip force are rare. In conscious monkey positive linear regression coefficients have been disclosed for both force and rate of force change in unidentified neurons, whereas the Purkinje cells decreased their firing with force (Smith and Bourbonnais 1981). In our investigation, similar to M1, the BOLD-signal increased linearly with the applied force in the ipsilateral anterior cerebellum, as recently suggested by Kuhtz-Buschbeck et al. (2008). According to somatotopical investigations of the cerebellum the localization of our activation clusters corresponds to the reported anterior hand representation (Dimitrova, et al. 2006; Grodd, et al. 2001; Rijntjes, et al. 1999). The anterior cerebellum is part of the spinocerebellum and has two main sources of afferents. It receives information from proprioceptors (muscle spindles, tendon organs) and skin, via the spinocerebellar tracts (Bushara, et al. 2001) and additionally descending information from motor areas, which conveys an efference copy of the on-going movement via the pontine nuclei (Kelly and Strick, 2003; Nowak, et al. 2007; Ramnani 2001, 2006). It is thus not surprising that the BOLD-signal in the anterior cerebellum behaves in a quite similar way to that in M1. It has been proposed that the cerebellum predominantly processes sensory information from the target muscles in order to optimise movements (Jueptner and Weiller, 1998; Kording and Wolpert, 2006; Nowak, et al. 2007). Therefore, the BOLD-signal may be not merely related to force generation and control but mainly caused by an additional recruitment in the sensorimotor feedback from muscle spindles and tendon receptors.

Non-linear relationship between BOLD-signal and power grip force

In S1, IPL, PM, and posterior cerebellum, the relationships between brain activation and power grip force were quite complex, either non-monotonic or showing modulations, which cannot be simply interpreted as force correlates.

Primary somatosensory cortex

The BOLD-signal in S1 did not correlate linearly with the applied force. Similar beta values were obtained for low force pulses of 10% and 20% MVC, and a significant increase was only observed for 30% MVC. Recent neuroimaging investigations suggest that the level of required attention is an important factor mediating cortical responsiveness (Arthurs, et al. 2004; Johansen-Berg and Matthews 2002; Rowe, et al. 2002). Moreover, early somatosensory evoked potentials (SEPs) in S1 were modulated during attended sensory-motor tracking (Legon and Staines, 2006). Thus, increased attention to the sensory feedback and, connected to this, increased processing of somatosensory signals in S1 during fine force control may have led to the nearly equivalent BOLD-signal observed for 10% and 20% MVC. Our findings

are not in accordance either with the significant positive correlation coefficients of static force in monkeys' S1 (Wannier, et al. 1991) nor with brain imaging data of Dai et al. (2001) showing a linear increase in number of activated pixels and average intensity in S1 with static handgrip force. These observations once more suggest that force is centrally controlled in different manners for the static and dynamic force conditions.

Parietal and premotor cortex

Our main finding was that relationships between the BOLD-signal and power grip force were complex and without any trend to linearity in both parietal and premotor areas bilaterally. Previous studies have suggested that parietal and premotor regions are involved in planning and on-line control of visually-guided movements (Ehrsson, et al. 2001, 2003; Elsinger, et al. 2006; Hamzei, et al. 2002; Ogawa, et al. 2006; Vaillancourt, et al. 2003, 2007). Thereby, the transformation of visual input into action is controlled by a neuronal circuit where the PM cortex receives visual information from the extrastriate visual cortex via parietal areas (Hamzei, et al. 2002). The essential role of the parietal cortex for dynamic, goal-directed sensorimotor integration suggested by Tunik et al. (2007) is supported by recent studies (Elsinger, et al. 2006; Vaillancourt, et al. 2007) demonstrating increased BOLD-signal either with frequent compared to less frequent, intermittent visual feedback or with external versus internally guided movements. Furthermore, parietal areas play an important role in the control of demanding motor tasks such as fine force control in precision grip (Ehrsson, et al. 2001). In line with these results, the stronger cortical activation in both IPL foci with 10% as compared to 20% MVC grip force, probably reflects the higher requirements in the precise control of low forces. This assumption is reinforced by the more frequent variability found at the individual level at our low force range. The predominant activation in the right posterior parietal cortex can be interpreted as involvement in conscious error evaluation, as suggested in a previous study using a visually-guided motor task (Ogawa, et al. 2006).

In PMv the relationship between the BOLD-signal and the applied force were almost identical to that in IPL. This can be explained by the fact that PMv receives projections from IPL, particularly from the AIP region, which is related to visuomotor control of the hand, in particular grasp (Hamzei, et al. 2002; Shikata, et al. 2003; Tanne-Gariepy, et al. 2002). The stronger cortical activity with 10% compared to 20% MVC found in both ipsilateral and contralateral PMv, as well as in the parietal lobe, is supported by earlier reports using force pulses and maintained grip force, which also describe stronger activation in these regions for small grip forces than for high ones (Ehrsson, et al. 2001; Kuhtz-Buschbeck, et al. 2001). Primate studies have revealed that the neuronal firing rate in PMv can correlate with isometric force in precision grip however; these correlations were clearly context-dependent (Hepp-Reymond, et

al. 1999). Our present findings provide further support to the suggestion of these previous studies that coding of force in PMv can be influenced by several factors.

Posterior cerebellum

In posterior cerebellum two main observations are worth discussing. First, the foci were bilateral and located mainly in lobule VIIA and Crus I, both belonging to the neocerebellum. According to several investigations these regions also have a hand representation, but mainly receive bilateral projections from premotor, prefrontal and parietal cortices through the pontine nuclei (Dimitrova, et al. 2006; Kelly and Strick, 2003; Rijntjes, et al. 1999). In other words, the posterior cerebellum appears to be essential for movement coordination (Ramani et al., 2001) and visuomotor transformation (Miall, et al. 2000; Vaillancourt, et al. 2003). Second, the BOLD-signal in the posterior cerebellar foci also did not correlate linearly with the production of dynamic force pulses. The slightly higher activation of 10% as compared to 20% MVC in the posterior cerebellum mirrors the cortical parietal and premotor activation and thus may reflect the more demanding sensory and attentional processing in visually-guided force production during the 10% MVC condition. This finding is in accordance with studies reporting the greatest activation under attention to action (Allen, et al. 1997; Indovina and Sanes, 2001) and during complex manipulation (Milner, et al. 2007). Moreover, Vaillancourt et al. (2006) showed increase in activation volume and percent signal change in the lateral posterior cerebellum with high frequency visual intermittent feedback during force control in precision grip. These previous observations corroborate our finding that posterior parts of the cerebellum are more strongly involved in the visuomotor processing rather than in simple force generation.

In conclusion, the current study on the generation of repetitive force pulses in power grip provides new insights on the neural organization of visually-guided force control. We have shown that cortical activation does not necessarily scale with increased grip strength and that force control in humans is differentially represented in the cortical and subcortical sensorimotor network. Our findings suggest that fine-graded forces are mainly controlled by M1 and the corresponding anterior cerebellar region. Activation in premotor and parietal cortical areas, as well as posterior cerebellum during the specific task is strongly modulated by visual input and context-dependent information. These observations may be of potential clinical significance in recovery following an infarct involving M1 in the sense that premotor and parietal cortical areas may poorly contribute to recovery in the control of low forces, whereas the anterior cerebellum with its direct peripheral input may play a primary role.

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3.4 Study 4

New Technologies and Concepts for Rehabilitation in the Acute Phase of Stroke: A Collaborative Matrix

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Abstract

The process of developing a successful stroke rehabilitation methodology requires four key components: a good understanding of the pathophysiological mechanisms underlying this brain disease, clear neuroscientific hypotheses behind the therapy, adequate clinical assessments of its efficacy on multiple timescales, and a systematic approach to the application of modern technologies to assist in the everyday work of therapists. Achieving this goal requires collaboration between neuroscientists, technologists and clinicians to develop well-founded systems and clinical protocols that are able to provide quantitatively validated improvements in patient rehabilitation outcomes. In this paper we present three new applications of complementary technologies developed in an interdisciplinary matrix for acute-phase upper limb stroke rehabilitation – functional electrical stimulation, arm robot assisted therapy and virtual reality based cognitive therapy. We also outline the neuroscientific basis of our approach, present our detailed clinical assessment protocol and provide indicative first results from patient testing of each of the three systems showing their viability for patient use.

Introduction

Stroke results in several neurological impairments which often severely reduce patient ability to perform activities of daily life (ADL) in both the short and long term. To individual patients, however, the assessments of impairments performed by attending physicians may be less important than maintaining or restoring premorbid daily-life functions. This is particularly true for upper extremity function and especially for skilled tool use. Constraint-induced movement therapy is a well-accepted, evidence-based approach for the chronic stage following a stroke (Taub et al. 1993; Taub et al. 1999). However, the optimal type of therapy for arm and hand function in the acute stage is still unclear, although a variety of treatment concepts has been defined (Kwakkel et al. 2004).

Evidence from animal trials suggests that early initiation of therapy favourably influences efficacy of rehabilitation. In the early post-stroke stages the brain already shows adaptive plasticity in within-system pathways (Biernaskie et al. 2004; Dobkin 2004). During this time the brain displays elevated sensitivity to rehabilitative experience. Also, there is evidence of association between early initiation of rehabilitation and better functional outcome as assessed by the Barthel Index (Paolucci et al. 2000). Other critical factors for sensorimotor therapy to induce long-term brain plasticity and improve functional outcomes are that the therapy is intensive (Nelles 2004), highly repetitive (Bütefisch et al. 1995), task-oriented (Bayona et al. 2005) and rewarded. This has been shown in a longitudinal study where therapy was applied early in a repetitive, task-oriented scenario to significantly improve long-term functional outcomes (Feys et al. 1998; Feys et al. 2004). Other experiments with healthy animal and human subjects suggest that repetitive task-oriented exercise alone will not drive cortical

plasticity; rather, some degree of motor learning is required (Hlustik et al. 2004 ; Plautz et al. 2000) such as that experienced by stroke patients undergoing rehabilitation.

These threads of evidence all point towards the need to develop arm and hand therapies for acute-phase stroke patients that are intensive, repetitive and oriented towards activities of daily life. The best methods and technologies to be used are as yet unknown and likely to vary between patients. In this study we are applying new rehabilitation technologies developed in a close collaboration among clinical, engineering and computer science groups interconnected in a "Rehabilitation Technology Matrix" within the Swiss National Center for Competence in Research (NCCR) in "Neural Plasticity and Repair".

Treatment Rationale and Goals

The primary goal of our approach is the multi-modal reactivation of sensorimotor mechanisms that are part of the disrupted motor program by stimulation of (undamaged) regions which project directly or indirectly to sensorimotor areas. At the lowest level, we achieve this by providing the afferent proprioceptive feedback to the central nervous system (CNS) that would be present during normal active movement execution, thus closing the motor control loop. At a higher level, we also aim to recruit motor planning and execution areas by embedding the movements in task-oriented scenarios. At the highest level, we can also stimulate motor planning areas by directing patient attention to a task and encouraging conceptual rehearsal of intended movements (Buccino et al. 2004). Simultaneously, we activate the action recognition system through visual input simulating the desired movement to provide feedback consistent with correct movement execution. Bilateral training using these techniques has also been shown to increase activation in motor cortex during the post-stroke acute phase (Staines et al. 2001) in contrast to the chronic phase, where constraint-induced therapy is the appropriate choice. Coupled bimanual coordination theory postulates that learning involves development of coordinative structures as the centrally linked upper extremities function together in solving motor tasks (Bernstein 1967).

The main secondary goal of our approach is to increase activity of the paretic limb through early, intensive and rewarded training of daily living functions, thereby motivating the patient to regain functional independence. The technologies we are deploying can play a key role in this process by replacing the physical strength of the therapist, providing for semi-automatic, objective performance evaluation, and/or enabling partially or completely unsupervised training. Additional benefits of this training regime include the elimination of non-use patterns of the affected limb through regular daily activity, prevention of compensatory maladaptive strategies, and avoidance of secondary acquired abnormal movements.

New Approaches - Technology Overview

Introduction

Conventional physiotherapy uses the decades-old method of peripheral manipulation performed by therapists, possibly with the help of mechanical devices or supports. The new methods we are investigating in this study – functional electrical stimulation (FES), exoskeleton arm robot (ARMin) therapy and cognitive virtual-reality (VR) based therapy – build on this methodology by assisting the therapist with the manipulation and measurement processes, and providing new possibilities for engaging the patient's peripheral and central nervous system (PNS/CNS). The main way in which the three systems differ from and complement each other is in the primary methods used to stimulate the PNS/CNS, ranging from peripheral manipulation (ARMin) through direct surface peripheral muscle stimulation (FES) to central nervous system stimulation (cognitive VR). These differences are summarised in Table 1.

	FES	**ARMin**	**Cognitive VR**
Movement control	System and patient, assistance possible Help arm support	System and patient Robot arm support	Patient only Table arm support
Movement range	Whole upper limb	Proximal (hand planned)	Whole upper limb
Data collection	Data glove	Force/torque and position sensors on robot arm	Digital compass, accelerometer, visual tracking, data glove
Task type	Real daily activities	Games & real daily activities	Games & simulated daily activities
	Unilateral	Unilateral	Bilateral
Task evaluation	Subjective human assessment	Objective software-based	Objective software-based
Nervous system stimulation	Specific external muscle stimulation plus observation of own arm (unilateral) Afferent proprioception	Peripheral limb manipulation plus observation of target stimuli Afferent proprioception	Central bilateral (virtual action observation via mirror neurons) Afferent proprioception if patient able to move
Unit cost	Low	High	Low

Table 1: Comparison of rehabilitation technologies.

In the following sections we describe each of the technologies in more detail.

Functional Electrical Stimulation (FES)

FES applies bursts of high intensity electrical pulses via surface (transcutaneous) electrodes to create action potentials in stimulated nerves, which cause muscle contractions. The Compex Motion stimulator (Popovic and Keller 2004, 2005) can be programmed to generate any arbitrary stimulation sequence that can be controlled and regulated. Each stimulator has four output channels; up to four channels (muscle groups) can be stimulated at a time. The stimulation sequences are stored on readily exchangeable memory chip-cards.

With this system we artificially generate muscle contractions required to perform a reaching and grasping task in subjects who have lost voluntary control of these muscles. As different stroke patients present with different disability to perform a reaching and grasping task we program the Compex Motion stimulator tailored to the patients` individual needs with regard to their lost or preserved motor function respectively. The electrode placement for elbow and finger extension is illustrated below in Figure 1.

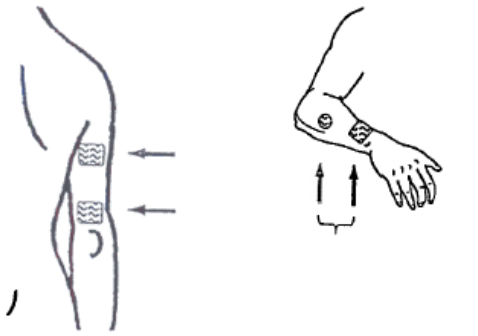

Figure 1: Electrode placements for functional electrode stimulation to extend the elbow (left) and finger (right).

Since we include patients with severe paresis a help-arm is used to partially balance the force of gravity on the arm. For hemiplegic patients, a typical combination of stimulated muscles is as follows: anterior deltoid muscle, triceps, extrinsic finger extensors, and extrinsic finger flexors. For tetraplegic patients, normally only distal muscles are stimulated, i.e. finger extensors, finger flexors, and thumb adductor. Depending on the decision of the therapists agonistic and antagonistic muscles can be stimulated. In principle, the method can be applied to subjects with severe spasticity. In order to overcome spasticity we apply pulses that have short pulse durations and therefore preferentially activate efferent nerves and not the afferents

that trigger hypertonic antagonist muscles {Keller, 2005}. However, we start with the FES training in the very acute state, in which the subjects have not yet developed severe spasticity.

Robot Assisted Rehabilitation and Measurement (ARMin)

Rationale

Manually assisted movement training has several limitations. The training is labour-intensive, and, therefore, training duration is usually limited by personnel shortage and fatigue of the therapist, not by that of the patient. The disadvantageous consequence is that the training sessions are shorter than required to gain an optimal therapeutic outcome. Furthermore, manually-assisted movement training lacks repeatability and objective measures of patient performance and therapy progress.

In contrast, with automated, i.e. robot-assisted, arm training the duration and number of training sessions can be increased, while reducing the number of therapists required per patient. Long-term automated therapy appears to be the only way to make intensive arm training affordable for clinical use. In the future, one therapist may be able to train two or more patients simultaneously. Thus, personnel costs can be significantly reduced. Furthermore, the robot provides quantitative measures, thus, supporting the evaluation of the rehabilitation progress.

Robot System Design

The robot is mounted to the wall with the patient sitting beneath (Figure 2). The patient's torso is fixed to the wheelchair with straps. A semi-exoskeleton solution was selected for the mechanical structure of the robot. The distal part of the robot is characterized by an exoskeleton structure, with the patient's lower and upper arm placed inside two shells moving the elbow joint. The upper arm is connected to an end effector-based structure moving the shoulder in three degrees of freedom. A six axis force sensor and four position sensors enable the robot to work in different patient-interactive control modes. The robot is designed primarily for the rehabilitation of incomplete spinal cord injured (SCI) and stroke patients.

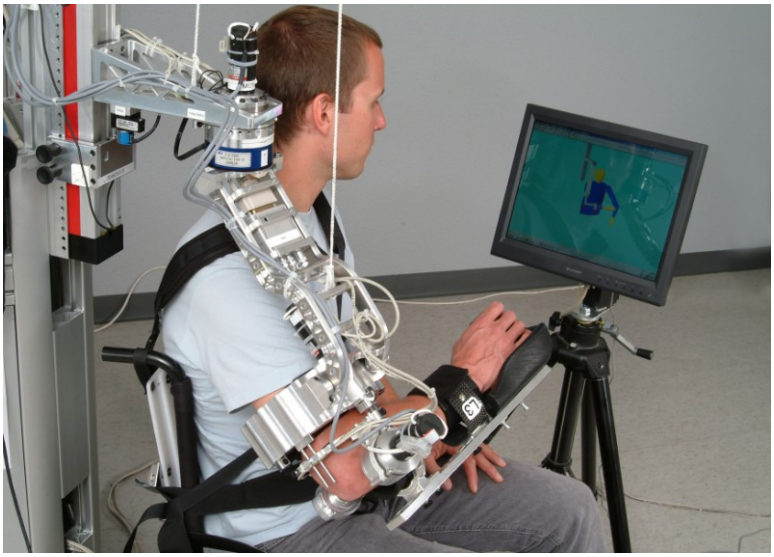

Figure 2: ARMin robot with a healthy test subject

Therapy Modes

ARMin allows three different therapy modes: movement therapy, activity of daily living (ADL) therapy and game therapy. The goal of the *movement therapy* is to prevent joint degeneration and to preserve joint mobility. In this mode, the therapist first guides the human arm together with the robot. The robot stores the movement and, then, repeats it with adjustable velocity. In the *ADL therapy* the subject can perform different tasks such as filling a virtual glass of water, grasping it and moving it towards the mouth (Figure 3). The purpose of the *game therapy* is to motivate the patient with simple games presented by an audiovisual display. In one game the user can move a virtual hand to intercept a ball which is rolling down a virtual plane (Figure 3). The robot supports the patient with just as much force as is needed. If the patient is not able to intercept the ball, the robot guides the patient's arm with an adjustable force right before interception.

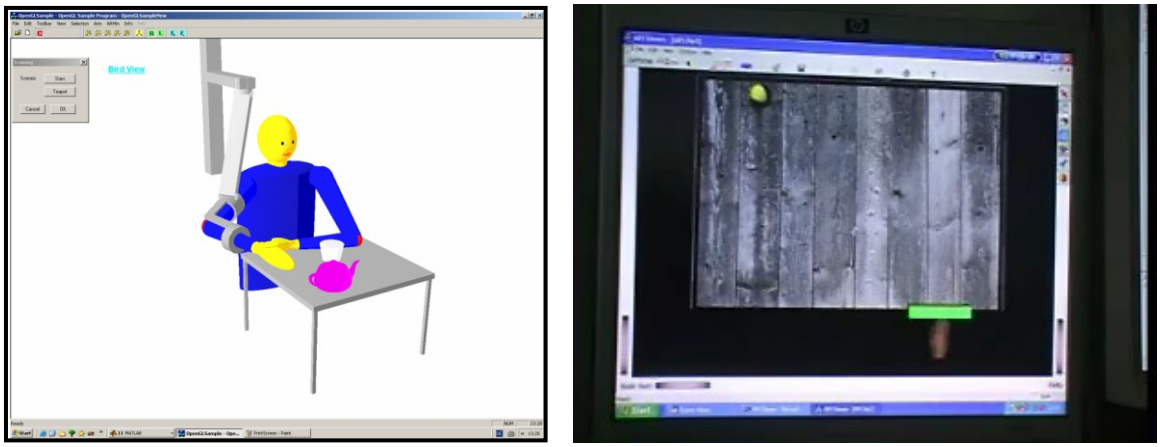

Figure 3: Visual scenarios for the ADL therapy mode (left) and game mode (right).

Virtual Reality Based Interactive Cognitive Therapy

The virtual reality (VR) based interactive cognitive therapy system is based on the idea that observing an action with intent to imitate engages similar neural circuitry to that used in actually performing an action – the so called "mirror neuron" hypothesis (Buccino et al. 2004). Indeed, there is evidence that such observation may even induce cortical plasticity under certain conditions (Stefan et al. 2005). In a rehabilitation setting, it thus seems reasonable that a system capable of appropriately stimulating the action observation system could encourage plasticity and repair during the post-stroke acute phase.

Our interactive multimedia system uses low-cost input devices such as consumer-grade data gloves (P5 data glove/Essential Reality, New York, USA) and digital compasses (HMR3300 (Honeywell)/Digi-Key Corporation, Thief River Falls, USA) linked to a multi-user 3D virtual environment (Torque/GarageGames, Oregon, USA) with visual and audio outputs. The system hosts a set of rehabilitation scenarios which are customisable to individual patient needs. The different scenarios provide a graded training programme of reaching and grasping for each patient, with online quantitative feedback about patient performance for enhancing motivation and monitoring patient progress. The initial scenarios being tested, in order of increasing difficulty according to patient progress, are:

1. *Hitting*: intercept virtual balls moving along a surface towards the patient by moving the arms.
2. *Catching*: intercept objects, with the additional constraint of "catching" them using the data gloves.
3. *Grasping*: move hands towards a virtual object, pick up the object, move it to a target location and release it.

In each scenario the patient sits in a chair with his/her arms on a table (Figure 4). The display is designed so that a three-dimensional rendering of two virtual arms appears in a similar orientation to the patient's real arms. Hand and arm movements detected by the input devices are mapped on to the movements of the virtual arms. This mapping can be adjusted by the therapist, and takes the form of scaling factors for the arm movements and/or left/right crossover mappings – ie. the non-paretic real arm can be used to control movements of the paretic arm. The patient performs the task while simultaneously trying to imitate the actions he/she observes in the virtual arms. The control of the movements of the "mirrored" arm can be gradually shifted from the intact arm to the paretic arm as the patient recovers, possibly accelerating further the speed of recovery.

Detailed position and event data from each game is recorded for analysis to both diagnose patient deficits and provide a record of improvement over training sessions.

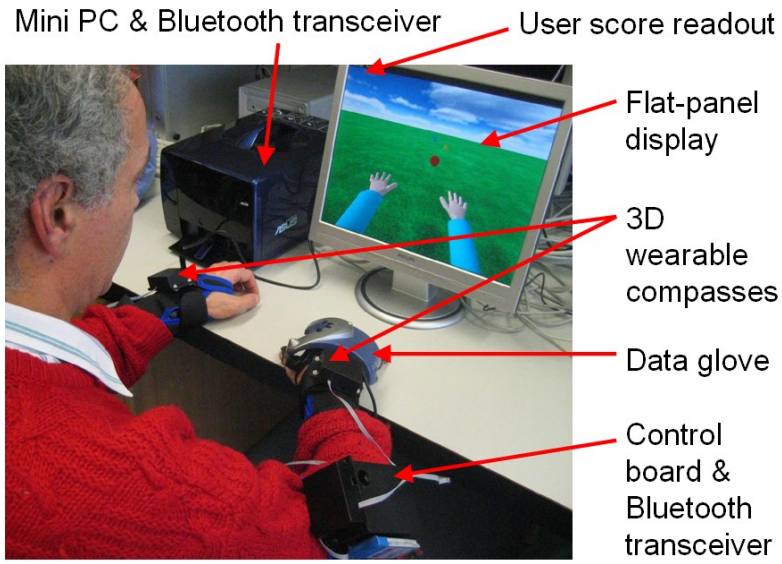

Figure 4: Virtual reality-based cognitive therapy system overview.

Control group

In the control group patients receive once daily basal task- and ADL-oriented physical therapy consisting of several modules such as vital (cardio-pulmonary etc.), static (posture, position etc.), mobility (transfer, gait etc.), and upper extremity functions. The rehabilitative effort available in the acute hospital (Neurology Department, USZ) is broadly similar to that in a rehabilitation hospital (Valens, Rheinfelden). The composition of the modules is the same between the Neurology Department and both rehabilitation clinics (vital: 0-5%, static: ~ 20%, mobility: 60-70%, upper extremity: 15-20%). One difference between the two, however, is that the time basis in the Neurology Department averages 1.5 hours versus 2 hours in the rehabilitation hospitals. Patients in the specific intervention groups receive daily basal task- and ADL-oriented physical therapy as described above. Additionally, concomitant therapies such as occupational therapy, logopedics, or neuropsychological therapies are offered to all patients depending on their individual needs.

Pilot Study – Treatment and Assessment Protocols

Treatment protocol

The therapeutic interventions are carried out once a day on 5 days per week during a period of 5 weeks. Each treatment session lasts 45 minutes. During their stay in hospital patients receive medical treatment according to their individual needs, including recombinant tissue–plasminogen activator (rt-PA), whenever applicable. All patients receive standard physiotherapy.

Assessment Protocol

Patients who will meet the entrance criteria are admitted into the trial during the first week after stroke onset. After initial clinical and functional assessment, patients are randomly allocated to either one of the experimental groups or to a control group. All procedures follow the ethical standards of the responsible institutional ethics committees. Informed consent is obtained from all patients participating in the study or from close relatives.

The timeline for patient treatment and evaluation is shown in Figure 5. Clinical parameters are evaluated before (1st, and 3rd day post-onset of stroke, baseline measurements B1, B2), midway (7th day, 3 and 6 weeks after stroke onset referred to as T1, T2, T3), after the intervention period (7 weeks after stroke onset referred to as A1), and during a follow-up, 3 (and / or) 6 months after stroke onset (F1, F2).

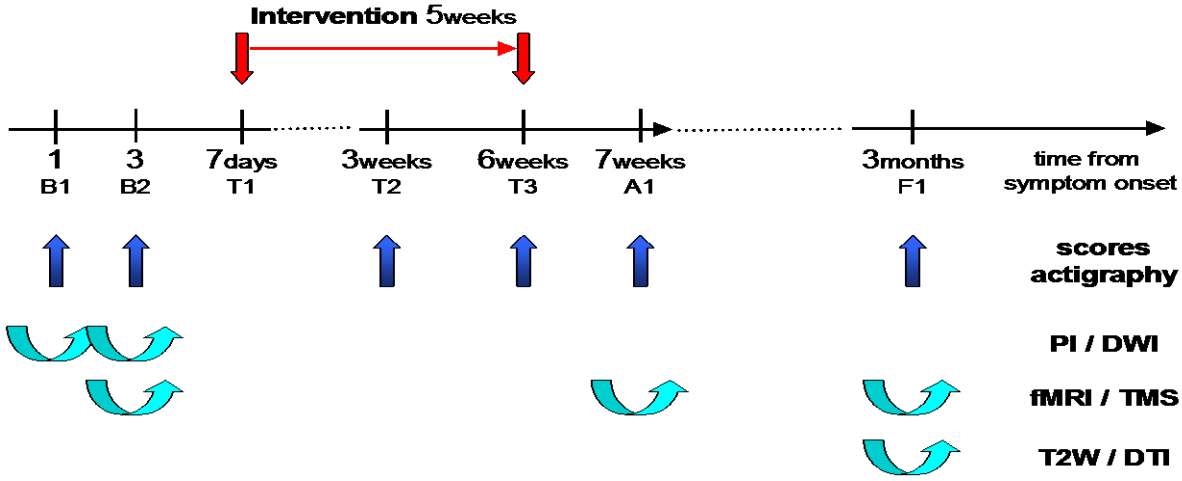

Figure 5: Timeline of patient behavioural evaluation.

Patient selection

Inclusion criteria

Stroke patients admitted to the emergency ward or stroke unit of the Neurology Department of the University Hospital Zurich (USZ) are screened for inclusion. The diagnosis of stroke is based on clinical history and examination and confirmed by MRI. The criteria for inclusion are:

1. diagnosis of acute ischemic brain damage in the first 48 hours after symptom onset
2. supratentorial localisation of the stroke (comprising cortical as well as combined cortico-subcortial localisation),
3. an obvious motor deficit of the hand with best hand function defined as Medical Research Council scale (MRC) ≤3 (effort against gravity) lasting until beginning of treatment
4. older than 18 years of age

5. alert and sufficient co-operation to permit full clinical examination, and
6. able to sit in a wheelchair or on a chair.

Exclusion criteria

Patients older than 80 years of age, with a previous clinical history of stroke or a pre-stroke disability affecting the arm are excluded. Furthermore, pregnant women and patients with major cognitive deficits (comprehension deficits, severe depression, dementia etc.), disturbances of basal sensibility which may not allow testing of the adequate electrical stimulation, epileptic seizures, progressive stroke, symptomatic intracerebral haemorrhage (ICH-associated increase of NIHSS > 4 points), severe rheumatoid illnesses restricting joint mobility of the upper extremities, skin injuries, rash, burns fresh scars, or inflammation on arms or hands, painful shoulder-hand-syndrome, shoulder subluxation (palpatory > 2 fingers), severe autonomic dysreflexia, i.e. requiring medication to treat autonomic dysreflexia, patients with metal implants, pacemakers or any other stimulation devices, prosthesis of bones or joints in the local region of treatment as well as patients with any severe medical diseases are also excluded.

Clinical (descriptive) assessment

At entry to the study, patient characteristics such as age, sex, side of paresis, site of lesion, type and onset of stroke as well as associated medical conditions are documented. On admission to stroke unit at the Neurology Department, USZ (B1) the NIHSS (Brott et al. 1989) as well as the MMSE (Folstein et al. 1975) are performed by clinicians involved in the routine treatment of the patients. The remaining acute neurological assessment (B1-B2) including neurological impairment, muscle strength, a detailed sensory examination, handedness, and neuropsychological examination of each patient are performed prior to randomisation. Information from sensory and cognitive tests is used for a post-hoc analysis studying the impact of the presence or absence of sensory deficits for functional recovery. After the intervention period (A1), and during the follow-up (F1), the overall outcome is assessed by the Modified Rankin Scale (MRS) (Bonita and Beagle 1988; Rankin 1957; van Swieten et al. 1988) in the Neurology Department of the USZ.

Outcome measures

Clinical scales

The primary outcome is evaluated on the activity level by the use of the Chedoke Arm and Hand Activity Inventory (Barreca et al. 2005). Three secondary outcome measures are employed to follow the levels of activity (extended Barthel Index (Mahoney and Bartel 1965; Schönle 1995) and participation (SF-36 (Anderson et al. 1996; Weimar et al. 2002), Motor

Activity Log (Taub et al. 1993; van der Lee 2004). All measures meet the criteria of reliability and validity. They are assessed before randomisation (B2), after transferral to rehabilitation clinic (Valens or Rheinfelden) after each treatment week and after the treatment period (A1, F1).

Behavioural evaluation

In addition to clinical scores, we assess behavioural data to follow up the functional recovery process of the paretic upper extremity (Figure 5). In the acute stage (B2), by the end of every treatment week as well as after the treatment period (A1, F1), we also use a drawing test to follow recovery progress more closely (Eder eta l. 2005). Actigraphy recordings from the contra- and ipsilesional arm yield additional data about the amount of spontaneous motor activity on predefined days over the whole observation period (Siekierka-Kleiser et al. 2006).

Functional brain alterations

Neuroimaging

Functional Magnetic Resonance Imaging (fMRI)

We use fMRI to study the evolution of activation patterns during the process of recovery. The dynamics of cerebral activation maps, especially their lateralization related to the course of motor recovery, showed changes during the course of motor recovery in several previous studies (Calautti et al. 2001; Calautti et al. 2001; Feydy et al. 2002). We therefore use the laterality index (LI) to quantify the amount of blood oxygenation level dependent (BOLD) activation between the ipsi- and the contralesional hemisphere (Cramer et al. 1997). Furthermore, we compare the activation pattern of the patients in individual and group analysis with healthy subjects matched for gender, age and manual dexterity (Keisker et al. 2006). Before (B2) and after (A1, F1) intervention we measure BOLD fMRI to test the activation of motor areas for the different trained interventions. The patients have to generate with each hand isometric repetitive force pulses of 20 % maximal voluntary contraction (MVC). In this block design, including 21 s of force condition alternating with 21 s of rest (5 repetitions), the subjects are guided by colour-coded feedback, where target and exerted forces are displayed on a screen in front of the subject.

Perfusion Weighted Imaging (PI), Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging Imaging (DTI)

In addition to fMRI we use our regular clinical protocol comprising perfusion and diffusion weighted imaging. Lesion volumetry of PI and DWI is based on automatic lesion outline at predefined thresholds relative to mean image intensity in the unaffected hemisphere (Neumann-Haefelin et al. 1999; Wittsack et al. 2002). T2-lesions are outlined manually by one of the authors.

Preliminary results

As of this writing, the studies are in progress and first results are appearing. Here, we summarise the results obtained to date for each of the three technologies being tested. Because only a few patients have been tested so far, between-subjects power calculations have not yet been performed. For equivalent total amounts of training per patient, large numbers of subjects per test group (n > 50) may be required to achieve statistically significant results due to the high between-subjects variability. However, we believe that because patient motivation to use the therapy technologies is high (as measured by user questionnaires), and they receive our therapies in addition to normal therapy, much smaller numbers of subjects per group will be required to show improved outcomes. This testing scenario is realistic because our therapies are designed to supplement rather than replace existing therapy, with only minor increases in staff loading because of the semi automated nature of the therapy systems. The main results we expect for each of the three technologies are improved functional recovery as measured by the ADL tests, and cortical activations that are more normal than in the control cases.

Functional Electrical Stimulation

Subjects after stroke with remaining upper limb deficits often suffer from abnormal flexion hyperactivity in shoulder, elbow and arm. It could be shown that FES can overcome these abnormal synergies in the elbow by stimulating the triceps muscle during reaching activities (Keller et al. 2005). For achieving functional use of the hand it is also necessary to be able to overcome similarly occurring abnormal hyperactivity in the fingers.

Preliminary tests of selectively activating the wrist and fingers movements against these abnormal patterns were performed in two stroke subjects. Both subjects (female) had a severe paresis of their right arm and hand, which resulted in a Fugl-Meyer score of 20/66 and 27/66. For selective activation of wrist and finger extensors by means of transcutaneous electrical stimulation three regions were found over the finger and wrist extensor muscles that resulted in differential wrist and finger movements. The goal was to activate finger extensor muscles with minimal ulnar and radial deviation in the wrist and to activate wrist extension with minimal activation of the finger extensors. This second strategy would allow stroke subjects to close their hands without compromising a natural wrist position achieved by stimulating the wrist extensors. Region 1 activated wrist extension combined with wrist radial deviation and some finger extension. Region 2 activated wrist extension combined with wrist ulnar deviation and some finger extension. Region 3 mainly activated the finger extensors with almost no ulnar/radial deviation and some wrist extension. In both subjects, activation regions could be found at moderate levels of stimulation (150 µs pulse width, 25 Hz stimulation frequency and amplitudes between 18-22 mA). To illustrate the results (see

Figure 6) the angular change of wrist and finger positions during selective stimulation of the three regions were measured with a P5 data glove (Essential Reality Inc.). All three regions were stimulated in consecutive order, first region 1, then region 2, and finally region 3. Each region was stimulated with the following pattern: 1 s amplitude ramp up, 5 s constant stimulation at moderate amplitude between 18-22 mA, 1 s amplitude ramp down with 1 second resting periods between patterns. Resting position before stimulation was 0° radial/ulnar deviation, 40° wrist flexion and 80° finger flexion. Stimulation of region 3 (for finger extension) showed almost no radial/ulnar deviation and more finger extension than stimulation of regions 1 and 2. Stimulation of region 1 resulted in wrist radial deviation and more index finger activation than ring finger activation. Conversely, stimulation of region 2 showed more ring finger activation than index finger activation. Both region 1 and 2 produced more wrist extension than region 3. On the other hand, finger extension, especially for the middle finger was partially reduced compared to stimulation of region 3. These results show that finger extension can be functionally stimulated to overcome paresis and flexion hyperactivity in the hands of subjects after stroke. In addition, the results indicate that a certain level of selectivity in wrist and finger extensor activation can be achieved with transcutaneous electrical stimulation.

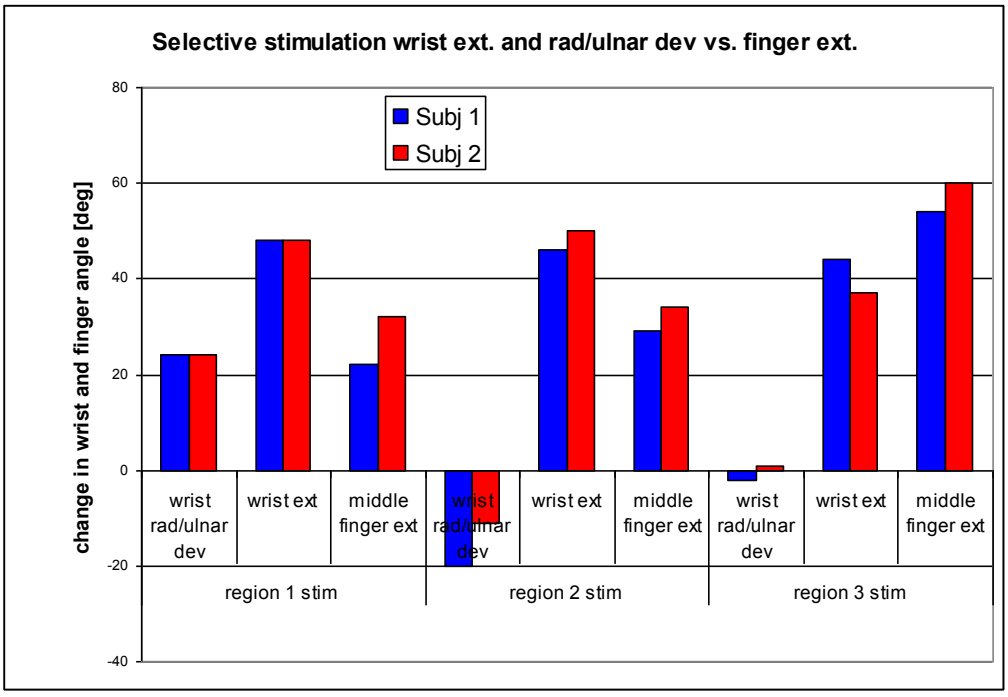

Figure 6: Kinematic wrist and finger angular data for selective electrical stimulation of the wrist and finger extensors using three activation regions over the wrist and finger extensors. The results indicate that simultaneous activation of region 1 and 2 produces co-contraction of radial/ulnar deviation and contraction of wrist extension with less activation of finger extension compared to the activation of region 3.

ARMin

A pilot study with ten healthy subjects and five chronic stroke patients was carried out to analyse comfort, functionality, acceptance, and whether the patients are able to perform the proposed tasks. With the five patients a series of sessions were performed, each including 30 min of movement therapy and 30 min of game therapy. The five patients used the robot for more than 30 hours altogether.

The fixation of a patient in the robot takes approximately 5 minutes. The robot can easily accommodate subjects with body sizes between 155 cm and 192cm. The robot allowed reliable trajectory recording and repetition with adjustable velocities during the movement therapy. During the game therapy it provided interactive support for the patient. Participants and therapists gave ARMin high grades with respect to comfort, design, and clinical usability. Although it was not the primary goal to study the therapeutic effect during the relatively short training sessions, an improvement of the patients' motor functions could be observed. From session to session the robot support decreased, while speed and range of motion increased and joint coordination improved. Thus, the patients could play games with increasing difficulty levels.

Figure 7 shows the results of a game therapy performed with two chronic hemiplegic subjects. The subjects had to catch a visually displayed ball (Figure 3) by moving their hand towards the ball. Subject A was able to catch all balls without any robotic support (the robot behaved transparent), whereas subject B needed some support to catch the balls. ARMin allows measuring the voluntary force of the subjects and storing it for later therapy assessment.

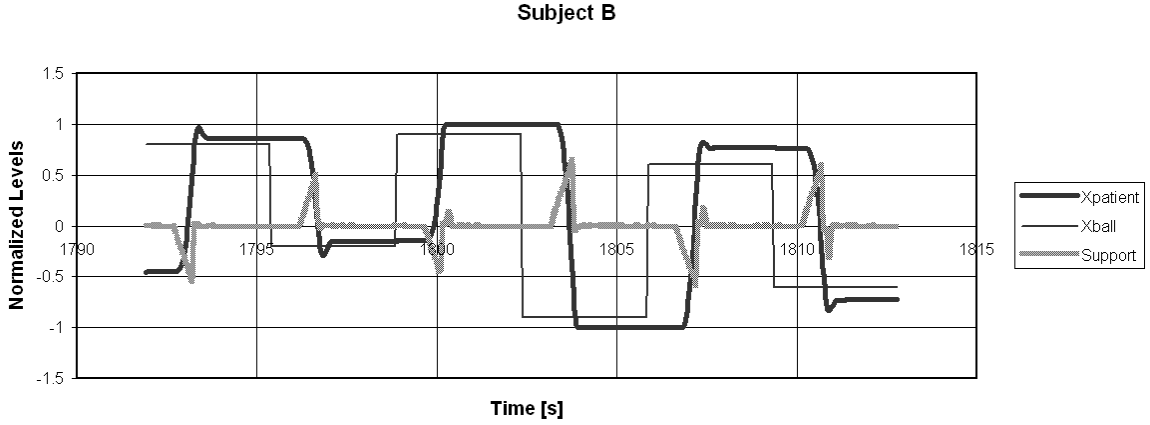

Figure 7: Movement and force support recorded from two hemiplegic subjects playing the ball game.

VR Cognitive Therapy

The VR cognitive therapy system has been implemented with the completed hitting scenario. This has been tested in pilot studies on the following groups of subjects:

- Healthy subjects, mean age 29 ± 4 years (N = 19, mean standard ± deviation), usability pilot
- Stroke patient, age 63 (N = 1), usability pilot
- Stroke patients, ages 62 and 56 (N = 2), usability and assessment pilot

Both the healthy subjects and the stroke patients were able to use the system to learn to perform the task within a short time after the commencement of the first test session. For the initial settings given (1 ball every 2.5 seconds, ball start location random or wave pattern), most healthy subjects and patients were able to intercept between 70% and 100% of the balls. User acceptance of the system was high (anecdotal and questionnaire responses); in particular the patients tested expressed a desire to use the system on an ongoing basis.

Figure 8 shows a plot of the data for a test run with one of the stroke patients, showing the movements of the left and right hands as well as the fates of each of the balls (caught with left hand, caught with right hand, or missed). In this example the balls appeared every 2.5 seconds in a wave pattern. It can be seen that most of the "miss" events occurred towards the extremities of movement, and that a greater proportion of the balls were missed on the left side than the right side. The patient's paretic side was the left side and the patient was right-handed when healthy, so the relative contribution of paresis and handedness to the left/right performance imbalance can only be assessed after further testing as the patient recovers left arm function.

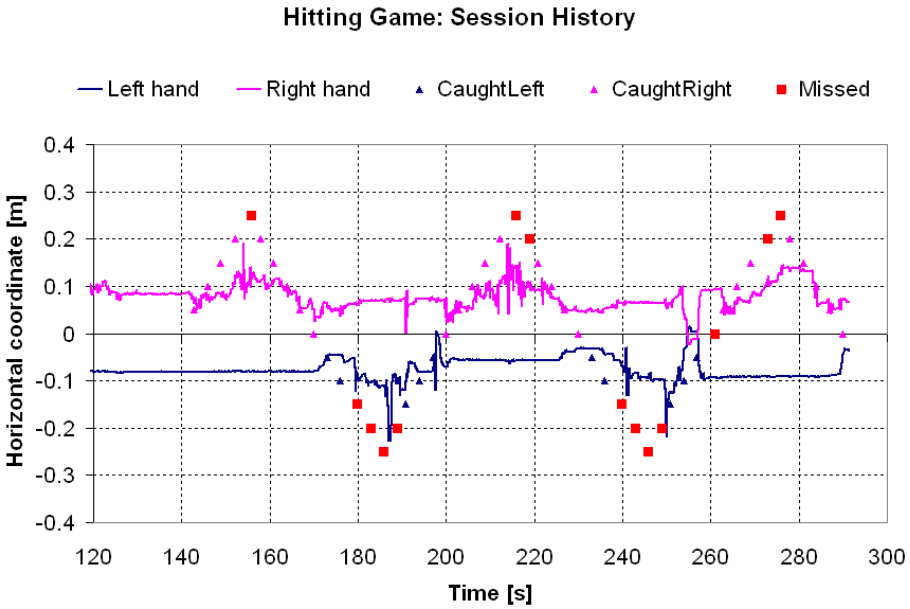

Figure 8: Sample session history from patient 1, usability and assessment pilot.

Figure 9 shows the performance of patient 2 from the usability and assessment pilot over successive therapy days. Each therapy session consisted of six sets of 50 balls each. The mean score on the last day was significantly higher than that on the first day (t-test, $p < 0.01$). As the patient had reached virtually perfect performance by the fifth day, continued therapy would probably have benefited from an increase in game difficulty (increased ball speed, increased dispersion of balls, etc.).

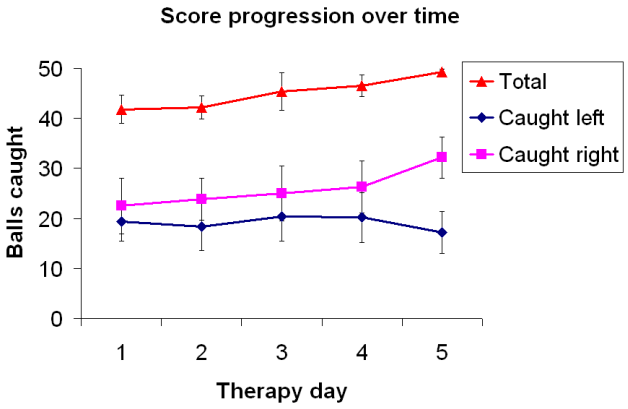

Figure 9: VR game performance over successive therapy days for stroke patient 2 of the usability and assessment pilot starting on the 7th day after symptom onset. Each therapy session consisted of six sets of 50 balls each. Error bar = ±1 standard deviation.

Figure 10 shows the change in cortical activation in a patient who underwent the VR cognitive therapy for two weeks. The patient was instructed to perform a right-handed grip strength task in the MRI scanner. The bilateral activation of M1 that was present shortly after the stroke changed significantly towards normal localized contralateral activation. The generality of this result, and the extent to which the VR cognitive therapy contributed to this result will be determined in future control tests with patients undergoing normal physiotherapy.

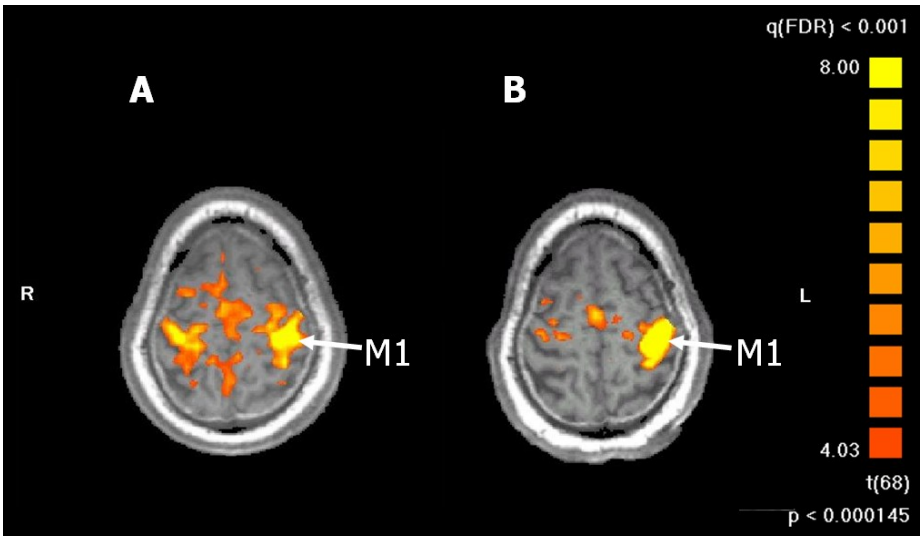

Figure 10: Changes of cortical activation as a function of intervention. Shown is involvement of M1 during dynamic force generation with the paretic right hand. A. Bilateral activation in the primary motor cortex (M1) before intervention. B. Contralateral activation in M1 3 months after intervention.

Conclusions & Outlook

Our interdisciplinary approach to the application of multiple technologies in a simultaneous study of their efficacy for stroke rehabilitation is enabling us to obtain a well-validated, consistent evaluation of each of our three complementary approaches to neuro-rehabilitation. This synchronised assessment of multiple new technologies in an extensive simultaneous clinical study is, to the best of our knowledge, a first in the field of neuro-rehabilitation. While some of our initial results from patient testing are promising, more data is required before we can make definitive statements concerning the efficacy of our different methods. The question of whether a combination of our new technologies is more effective than any single method is open, and should be the subject of a future study.

Acknowledgments

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4 General discussion

The present work was conducted to make a contribution to the ongoing debate how the brain masters damage in terms of plastic processes and how the reorganization pattern are related to the functional recovery. The aim of this thesis was to investigate plastic processes in the language and sensorimotor network following acute (vascular) and chronic (tumour) brain damage. Although many studies investigated the cortical activation pattern and the corresponding functional recovery in patients with brain lesions in either the language or the sensorimotor network, there is still a debate about whether improvement represents sparing or restoration of function in perilesional zones of the ipsilesional hemisphere or recruitment of homologous contralesional regions. These issues are still unclear in the field of language and motor functions which share many aspects of functional reorganization. We were therefore interested to learn more about language *and* motor reorganization to both compare and differentiate the two processes against each other. Furthermore, we aimed at comparing functional reorganization in stroke and tumour patients because acute brain lesions cause damage to the brain within the time range of hours or days with probably different impact on language function than tumours, which slowly grow allowing a progressive redistribution of eloquent sites. Pivotal for the interpretation of reorganization pattern in patients is the preceding assessment of the corresponding functions in healthy subjects to consider aspects of individual variability and task dependent differences in the neural representation of language and motor processes. Therefore we conducted two studies (1,3) where we investigated language and motor tasks in healthy subjects which were then assessed in patients with damage in the language (tumour and stroke, study 2) and sensorimotor network (study 4). Furthermore, the influence of additional therapeutical intervention (e.g. interactive cognitive therapy) on functional recovery and the corresponding activation pattern was assessed in patients from the acute state to a follow up period of three month (study 4).

The main aims of this thesis were:

- To map language and motor processing in healthy subjects in order test the stability of the task specific activation pattern and to consider inter-individual variety. (study 1 and 3).
- To map plastic processes of language function following brain damage and to compare different etiologies of brain lesions and its impact on the reorganization and functional recovery (study 2).
- To map plastic processes of sensorimotor function from the acute state to a follow up period of three months after therapeutically intervention (study 4).

The main findings of the above presented studies will be outlined and integratively discussed.

In the first study, entitled *Mapping of visual and auditory language processing by means of an fMRI protocol* we used two language tasks in order to identify the distributed neuronal networks involved in visual and auditory word retrieval, with the aim of providing sound evidence that the two tasks qualify as fMRI protocol for (presurgical) language mapping. The study demonstrated that the two tasks activate overlapping responses in perisylvian areas with both modalities, but there were also notable differences, pointing to an input specific and task dependent representation of language. The second study with the title *Mapping of brain plasticity in stroke and tumour patients*, assessed patients with vascular brain lesions in the chronic stage and patients with brain tumours before and after surgical intervention with two fMRI language paradigms, described in study 1. The converging results have shown that reorganization patterns in stroke and tumour patients often include perilesional and right hemispheric language related areas with however different levels of effective functional recovery. The various behavioural deficits were dependent on the task itself (picture-word matching versus lexical decision), parts of the task demands (e.g. matching versus non-matching picture and word), input modality, and lesion site. There was no apparent difference in the reorganization pattern between stroke and tumour patients in terms of reorganization patterns and the corresponding functional recovery. Effective integration of right hemispheric language related areas was observed in both groups, although there is a tendency for better behavioural performance in tumour patients.

In study 3 entitled *Differential force scaling of fine-graded power grip force in the sensorimotor network,* a visually guided motor task was designed to test the cortical representation of dynamic force generation with three different force grades (10%, 20%, 30% maximal voluntary contraction MVC). Brain responses were observed in the entire cortical and subcortical sensorimotor network and significant force-related modulation in several regions, including primary motor (M1) and somatosensory cortex, ventral premotor and inferior parietal areas, and cerebellum. The BOLD-signal however, increased monotonically with force only in contralateral M1 and ipsilateral anterior cerebellum. The remaining regions were activated with force in various nonlinear manners, suggesting that other factors, such as visual input, attention, and muscle recruitment also modulate the BOLD-signal in this visuomotor task. These observations may be of potential clinical significance in recovery following an infarct involving M1 in the sense that premotor and parietal cortical areas may poorly contribute to recovery in the control of low forces, whereas the anterior cerebellum with its direct peripheral input may play a primary role. In the fourth study with the title *New technologies and concepts for rehabilitation in the acute phase of stroke: a collaborative matrix,* three new applications of complementary technologies for acute phase in upper limb stroke rehabilitation are presented

and reorganization of the sensorimotor network were assessed by means of the in study 3 presented fMRI motor task. The developed therapeutically interventions are functional electric stimulation, arm-robot assisted therapy and virtual reality based cognitive therapy. Preliminary results from patient testing and activation pattern during the visually guided motor task in the acute stage and three month after therapeutically intervention showed a shift of the force related activation from bilateral to more ipsilesional side in the primary motor cortex. Additionally, an over recruitment in the premotor cortex (PM), supplementary motor area (SMA), inferior frontal gyrus and cingulate motor areas (CMA), in the parietal cortex (PAR) and in the cerebellum (CB) progressed to a more or less normal activation pattern of the sensorimotor network. These changes correlated with improved motor function of the hand in these patients.

4.1 Language functions and plasticity

The findings of study 1 revealed overlapping responses in perisylvian areas across tasks and input modality, but there were also notable differences, pointing to an input specific and task dependent representation of language. The identification of the neuronal networks involved in visual and auditory word retrieval allowed for a better understanding of the observed reorganization pattern in the stroke and tumour patients investigated in study 2.

The converging results of study 2 provide evidence that reorganization following brain damage in stroke and tumour patients often includes perilesional and right hemispheric language related areas that support the spared network and help to overcome disconnected language systems. All patients showed recruitment of perilesional areas implying that these regions are preferentially activated to restore lost function. However, in contrast to pervious findings, no apparent difference between stroke and tumour patients was found in terms of reorganization patterns and the corresponding functional recovery. The observation that the additional recruitment of right hemispheric language related areas differentially correlated with functional improvement depending on pre-morbid language organization, site of the lesion, task-demand and time since onset is supported by previous studies (Price et al. 2001; Raboyeau et al. 2008). In general, the integration of homologous structures seems to offer a crucial strategy in the process of cerebral plasticity, which also points to the relevance of this probably underestimated hemisphere in language processing of both healthy and brain damaged individuals. Both empirical evidence (including our present work of study 1) and frameworks of the functional anatomy of speech processing in healthy individuals suggest that the neural network supporting speech perception varies as function of the task and sometimes includes right hemispheric language related structures (Hickok and Poeppel 2007; Price 2000; Scott

and Wise 2004). This further strengthens the relevance of a differential view on language processing in healthy individuals and brain damaged patients.

4.1.1 Models of plastic reorganization following brain damage in the language network

There are models of functional compensation of language with regard to either the *progress* of reorganization from acute to chronic phase (stroke patients) or models that consider the *patterns* of reorganization in comparison to functional recovery (stroke and tumour patients). Saur et al. (2006) found three consecutive phases of recovery correlating with improved language function: a strongly reduced activation pattern of remaining left language areas and a loss of function in the acute phase followed by an additional recruitment of homologous language areas and finally a return to a predominant left hemisphere activation in the chronic phase with consolidation and normalization of language function. Looking at different reorganization patterns in comparison to functional recovery from a static point of view, the hierarchical model of functional compensation suggested by Duffau (2008), implies a recruitment of ipsilesional (especially peri-lesional) areas before the recruitment of contralateral homologous regions.

Although most of these models seem to be predominantly valid for patients with pre-morbidly left lateralized language organization, there are studies that report right-hemispheric integration associated with improved language function in the acute and chronic state and before intensive therapeutical intervention within the chronic state (Winhuisen et al. 2005, 2007; Richter et al. 2008). In this context it is debated whether the additional right hemispheric recruitment is due to a greater right hemispheric language function before the onset of the brain lesion or because of the reliance on additional cognitive and linguistic resources which are not required by normal subjects during linguistic processes (Cappa 2000). Furthermore additional right hemispheric activation has also been interpreted as phenomenon of transcallosal disinhibition probably reflecting less recovery than anomalous response caused by damage to the left hemisphere (Winhuisen et al. 2007; Price and Crinion 2005).

Effective plastic reorganization in *tumour* patients tends to me more often related to the inclusion of right hemispheric language related areas, because tumour growth is slow and allows a progressive redistribution of eloquent sites. In addition, patients who have no highly lateralized language network pre-morbidly, probably show good recovery of language functions in spite of (extensive) damage to the left hemisphere. Similarly to the reorganization processes observed in stroke patients, cerebral plasticity in tumours can be described by a model of hierarchically organized processes (Duffau 2008; Heiss and Thiel 2006): After small brain damage the restoration of the original activation pattern within the perilesional network of the dominant hemisphere shows best recovery of function. Intra-hemispheric compensation by secondary centres of the ipsilateral network sometimes leads to incomplete, but also often to

satisfactory improvement of language function. Inter-hemispheric compensation involving homotopic contralesional areas contributes to some improvement in function, but is usually not as efficient as the above described compensatory mechanisms, except in patients with slowly growing tumours where language function can be shifted to the right hemisphere (Thiel et al. 2006).

4.1.2 Summarizing model of plastic reorganization following brain damage in the language network

The above described findings of previous studies and the present work suggest that the appraisal of the manifold aspects of functional recovery following brain damage may help better understand the heterogeneous pattern of cerebral plasticity (see also Lazar et al 2008). In this sense Figure 13 tries to summarize the above discussed findings of the literature and the present work. Thereby, the three circles represent the different cortical activation pattern observed in the progress of functional reorganization and their impact on functional recovery. Initially, contralateral language related areas seem to be mainly recruited during language processing while (additional) ipsi- and perilesional activation can be observed at a later stage of functional recovery. In some cases (also depending on the pre-morbid language lateralization), there is a return to a predominant left hemisphere activation in the chronic phase. The transition from yellowish to reddish color within the circles reflects the differential influence of task demand and lesion site on the cortical activation pattern and its functional efficacy. E.g. reddish color in the “contralesional circle” corresponds to contralesional (contralateral) activation which is more effective in task x compared to contralesional activation in task y (yellowish color in the “contralateral circle”). The overlapping regions of the three circles represent the combination of different patterns and also reflect the interaction of different brain regions to overcome disconnected functional networks.

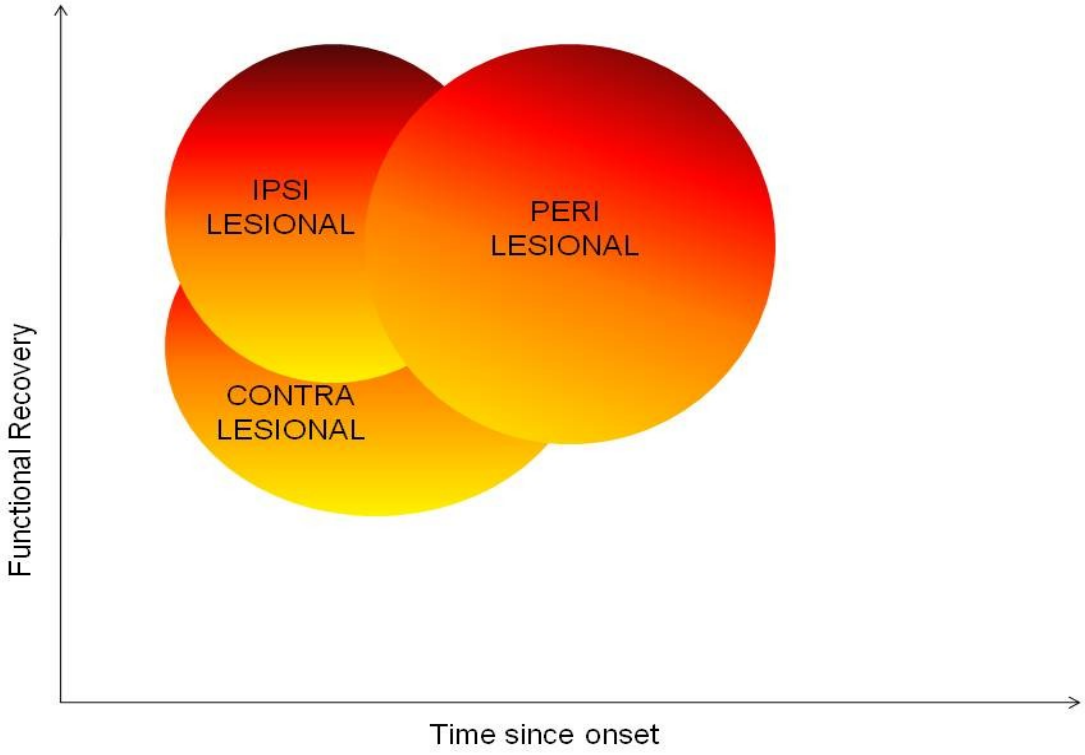

Fig 13. Summary of findings of previous studies and of the present work. Different cortical activation pattern observed in the progress of functional reorganization and their impact on functional recovery are represented by the three circles. Contralateral language related areas seem to be mainly recruited in the initial phase while (additional) ipsi- and perilesional activation can be observed at a later stage of functional recovery. In some cases, there is a return to predominant left hemisphere activation in the chronic phase. The transition from yellowish to reddish color within the circles reflects the differential influence of task demand and lesion site on the cortical activation pattern and its functional efficacy. E.g. reddish color in the "contralesional circle" corresponds to contralesional activation which is more effective in task x compared to contralesional activation in task y (yellowish color in the "contralateral circle"). The overlapping regions of the three circles represent the combination of different patterns and also reflect the interaction of different brain regions to overcome disconnected functional networks.

4.2 Sensorimotor network

Our findings of study 3 show that cortical activation does not necessarily scale with increased grip strength and that force control in humans is differentially represented in the cortical and subcortical sensorimotor network. Fine-graded forces are mainly controlled by the primary motor cortex and the corresponding anterior cerebellar region, whereas activation in premotor and parietal cortical areas, as well as posterior cerebellum is strongly modulated by visual input and context-dependent information. These findings provide new insights on the neural organization of visually-guided force control and may be of potential clinical significance in recovery following an infarct involving the primary motor cortex in the sense that premotor and parietal cortical areas may poorly contribute to recovery in the control of low forces, whereas the anterior cerebellum with its direct peripheral input may play a primary role.

The fourth study assessed three new applications of complementary technologies for acute phase in upper limb stroke rehabilitation. The developed therapeutically interventions are functional electric stimulation, arm-robot assisted therapy and virtual reality based cognitive therapy. While some of the initial results from patient testing are promising, more data is required before definitive statements concerning the efficacy of the different methods can be made. The question whether a combination of these new technologies is more effective than any single method is open and should be the subject of a future study. A patient who undervents virtual reality cognitive therapy for two weeks showed change of cortical activation. The bilateral activation of the primary motor cortex during the visually-guided motor task, which was assessed in study 3, was present shortly after the stroke, but changed significantly toward normal ipsilesional activation. This shift of activation correlated with improved performance of the hand. The generality of this result, and the extent to which the VR cognitive therapy contributed to this result will be determined in future control tests with patients undergoing normal physiotherapy.

Models of reorganization in the sensorimotor network following stroke suggest, similar to the models of language processing, that successful recovery is often related to recruitment of ipsilesional functional areas and whereas involvement of contralesional homologues is said to be less effective for functional recovery (Bütefisch et al. 2005; Calautti and Baron 2003; Hallett 1999; 2001; Hendricks et al. 2002; Rossini et al. 2003; Ward 2004; Weiller et al. 1999). In contrast to the language system, which tends to be left lateralized in many people, the strongly bilateral representation of the sensorimotor network may has a differential impact on the reorganization pattern and the functional recovery, because the functions of the lesioned area are progressively adopted by parallel motor circuits. These parallel circuits may originate from the contralateral, undamaged primary motor area, bilateral premotor areas, bilateral supplementary motor areas and bilateral somatosensory areas. As long as efferent, cortico-spinal output pathways exist, reorganization will predominantly evolve in the involved functional network (Pascual-Leone et al. 2005). In terms of the progress of plastic reorganization from the acute to the chronic state, the initially right-hemispheric recruitment of contral-lesional areas is suggested to shift to the ipsilesional side which is also supported by our preliminary results.

The findings of previous studies and our own work suggest that the above sketched model of brain plasticity in the language network (Fig 13) can be adapted with slight changes. In that there is also an (additional) recruitment of contralesional hemispheric structures during motor tasks in the acute phase after stroke followed by a shift of activation to the ipsilesional hemisphere. The return to strongly lateralized activation to the ipsilesional hemisphere can be

more often observed in the motor network than in the language network. This is probably due to the distributed and overlapping representations of single extremities and their corresponding movements (Indovina and Sanes 2001), which allows an excellent restoration of the functional network *within* the lesioned hemisphere.

In conclusion plasticity in the language and motor network share many aspects of reorganization in the progress of functional recovery. However, recovery from brain damage in the motor network may benefit from multiple parallel functional representations of movements. In the language network, pattern of reorganization and the corresponding behavioural performance maybe more strongly influenced by task demand, time since onset and lesion site. This has also an impact on the generalization of findings for clinical diagnosis and treatment, e.g. it is hard to find and investigate large groups of aphasics that are homogenous in terms of lesion site or neurological deficits. Therefore it is necessary to do further research on normal and abnormal functional anatomy and connectivity of brain regions (also including the application of additional methods as diffusion tensor imaging) in order to better understand the many neuronal pathways that are available to sustain each type of language and motor task.

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6 Curriculum Vitae

Career / Education

6.2010 - 10.2010	**King's College, London, United Kingdom** Visiting scientist with a grant of the University Zürich (Nachwuchsförderungskredit) Research at the Natbrainlab at the Institute of Psychiatry, King's College, London on invitation by Dr. med. M. Catani
11.2008 - 5.2010	**San Raffaele Scientific Institute Milano, Italy** SNSF-Fellowship for prospective researchers at the San Raffaele Scientific Institute on invitation by Prof. Dr. med. S. Cappa and Dr. M. Tettamanti
11.2008	**Dr. Phil., University of Zurich** "Functional recovery of sensorimotor and language networks in patients with acute (sensorimotor) and chronic (language) vascular lesions". Members of the Steering Committee: Prof. Dr. A. Linke, Prof. Dr. L. Jäncke, Prof. Dr. med. S. Kollias, Dr. M. Meyer
9.2008	**PhD in neuroscience, University of Zurich and ETH Zurich**
5.2005 - 10.2008	**University Hospital Zurich, Institute of Neuroradiology** Doctoral student
4.2004 - 9.2008	**University of Zurich and ETH Zurich, Switzerland** International PhD Program in Neuroscience
12.2003	**Master of Arts, University of Zurich** Master of Arts UZH in German and English language and literature
2.1998 - 11.2003	**University of Zurich** Student German and English language and literature
9.1994 - 9.1997	**University of Neuchatel and Berne** Medical Student, University Neuchatel and Berne
1988 - 1993	**Kantonschule Wattwil, St. Gallen**

Complementary activities

2.2005 - 6.2006	**Peer Mentoring** Nachwuchsförderung für WissenschaftlerInnen
5.2004	**PhD Training, Charité University, Berlin, Germany** PhD Training in Human Neuroimaging and Ethics of Neuroscience

Teaching

SS2007/SS2008	**ZNZ - Zentrum für Neurowissenschaften Zurich** ZNZ-Neuroimaging Course; data acquisition and analysis
2007	**University Hospital of Zurich** Educational training for radiographers
2007 - 2008	**Co-supervision of the master thesis:** "Eine fMRI Studie zur hemispärenspezifischen Verarbeitung semantischer Mehrdeutigkeit auf Wortebene"
2006 - 2008	**Co-supervision of practical trainings for undergraduate students**

Publications

Keisker, B., Hepp-Reymond, M-C., Blickenstorfer A., Kollias, S.S. 2010. Differential representation of dynamic and static power grip force in the sensorimotor network. Eur J Neurosci. Volume 31 (8):1483 - 1491.

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Keisker, B., Meyer, M., Kollias S., Weniger D., (in revision). Mapping of language processing for pre-surgical planning with a multimodal fMRI protocol.

Keisker, B., Chevrier E., Hepp-Reymond M-C., Kiper D., Kollias S.S, Eng K. (submitted). Neural correlates of interaction-induced ownership of virtual limbs in virtual reality.JNeurosci.

Keisker, B., Cappa S., Tettamanti M. (in prep). Bottom-up and top-down interaction during figural and lexical ambiguity processing.

Keisker, B., Cappa S.,Kollias S. Tettamanti M. (in prep.). The neural correlates of figural and lexical ambiguity processing.

Keisker, B., Hurschler, M., Weniger D. Jäncke L., Meyer M., (in prep.). Neural correlates of lexical-semantic ambiguity processing of polar homonyms: an fMRI study.

Siekierka, E.M., Eng, K., Bassetti, C., Blickenstorfer, A., Cameirao, M.S., Dietz, V., Duff, A., Erol, F., Ettlin, T., Hermann, D.M., Keller, T., **Keisker, B.**, Kesselring, J., Kleiser, R., Kollias, S, Kool, J.P., Kurre, A., Mangold, S., Nef, T., Pyk, P., Riener, R., Schuster, C., Tosi, F., Verschure, P.F., Zimmerli, L., 2007. New technologies and concepts for rehabilitation in the acute phase of stroke: a collaborative matrix. Neurodegenerative Diseases, 4 (1): 57-69.

Blickenstorfer A., Kleiser R., Keller T., **Keisker B**., Meyer M., Riener R., Kollias S., 2008. Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. Hum Brain Mapp 30(3):963-75.

Hägni, K., Eng, K., Hepp-Reymond, M-C., Holper, L, **Keisker, B.**, Siekierka, E. and Kiper, D. The Effect of Task and Ownership on Time Estimation in Virtual Environments. Presence 2007, Barcelona, Spain. Ed.: Moreno, Laura. Starlab Barcelona S.L.

Hägni, K., Eng K, Hepp-Reymond,M-C., Holper, L., **Keisker B.**, Siekierka, E., Kiper, DC., 2008. Observing Virtual Arms that You Imagine Are Yours Increases the Galvanic Skin Response to an Unexpected Threat. PloS ONE. 3(8): e3082. doi:10.1371/journal.pone.0003082

Posters at international conferences

Keisker, B., Cappa, S., Kollias, S., Tettamanti, M., The neural correlates of lexical and figural ambiguity processing. OHBM, Barcelona 2010.

Keisker, B., Hepp-Reymond, M-C., Kiper, D., Kollias, S.S., Eng, K., Neural correlates of ownership of virtual limbs. Society for Neuroscience, Chicago 2009.

Keisker, B., Meyer M., Kollias S., Weniger D., Mapping of language processing for pre-surgical planning with a multimodal fMRI protocol. FENS Geneva 2008.

Keisker, B., Kollias, S.S., Weniger D., The cerebral reorganization of language after damage: At the crossroads of neuroimaging and cognition. CNS New York 2007.

Keisker, B., Kleiser, R., Blickenstorfer, A., Hepp-Reymond, M-C., Kollias, S.S., Differences in cortical activation during static and dynamic power grip force. INS Zurich 2006.

Keisker, B., Kleiser R., Blickenstorfer, A., Hepp-Reymond, M-C., Kollias, S.S., Differences in cortical and cerebellar force control? OHBM, Florence 2006.

Keisker, B., Kleiser, R., Blickenstorfer, A., Hepp-Reymond, M-C., Kollias, S.S., Differences in cortical activation during static and dynamic power grip force. OHBM, Florence 2006.

Talks

Keisker, B. Mapping of brain plasticity of motor and language networks following brain damage: fMRI investigations, National Institutes of Health (NIH), Bethesda/Washington DC, 27.05.2008.

Keisker, B. Patterns of recovery are modulated by task demands, SGNR, Aarau, 27.10.2007.

Keisker, B. Mapping of brain plasticity of motor and language networks: fMRI investigations, Neuroradiologisches Kolloquium über funktionelle Magnetresonanz, Zurich, 17.01.2007.

Keisker, B. Differences in cortical activation during static and dynamic power grip force, NCCR meeting, Ittingen, 3.03.2006.

Keisker, B. Changes in brain activation during visually guided force generation after feedback removal, SGNR / SSN Basel, 28.01.2006.

Keisker, B. Motor fMRI experiments for the assessment of rehabilitation treatment, Neuroradiologisches Kolloquium über funktionelle Magnetresonanz, Zurich, 02.11.2005.

Keisker, B. Differences in cortical and cerebellar force control? ZNZ Symposium, Zurich, 21.10.2005.

Keisker, B.. Reparaturverhalten im Gespräch zwischen Aphasikern. 3. Jahrestagung der Gesellschaft für Aphasieforschung und –behandlung, Leipzig. 08.11. 2003.